Internal Clinical Guidelines Team

Document information (i.e. version number etc)

Tuberculosis

Clinical diagnosis and management of tuberculosis, and measures for its prevention and control, incorporating PH37 Tuberculosis - Hard to reach Groups

NICE NGxxxx

Methods, evidence and recommendations

Issue date: xxxx 2015

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

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Contents

Background

In 2006 the National Collaborating Centre for Chronic Conditions published guidance on the clinical diagnosis and management of tuberculosis (TB), and measures for its prevention and control. The section on the diagnosis of latent TB was updated (CG117) by the Short Clinical Guidelines team within NICE in 2011. Grey bars in the right hand margin indicate whether the section was updated in 2011 or is from the original guideline (2006). Sections highlighted in pink have been updated by the Internal Clinical Guideline team within NICE in 2015. In 2012, the Centre for Public Health team within NICE published public health guidance on 'Identifying and managing tuberculosis among hard-to-reach groups' (PH37), which has been incorporated into NCxx. Recommendations have been either updated, or adapted and incorporated as required. Similarly, some recommendations from CG117 have been not been updated but instead have been incorporated into NCxx alongside recommendations that have been updated.

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1 Introduction & summary section

1.1 Background information [2011, updated 2015]

This guideline makes recommendations on the prevention, diagnosis and management of latent and active TB, including both drug susceptible and drug resistant forms of the disease. It covers the organisation of relevant TB services. It relates to activities undertaken in any setting in which NHS or public health services for TB are received, provided or commissioned in the public, private and voluntary sectors.

The NHS and Public Health England have already begun work to reduce the harm caused by TB to many individuals and communities. TB is now a notifiable disease, meaning that clinicians have a statutory duty to notify Local Authorities or a local Public Health England Centre of suspected cases, and efforts have been made to strengthen services and ensure clear lines of accountability and responsibility. However, a stronger approach to TB control is now needed in order to build on this work. Indicators of TB incidence and TB treatment outcomes have been included in the Public Health Outcomes Framework[1], and a collaborative TB control strategy has been designed that brings together best practice in clinical care, social support and public health. Agencies at all levels – including national and local government, clinical commissioning groups and third sector partners – are now committed to working in partnership to decrease the incidence of TB, fight the spread of drug resistant forms of the disease, reduce current health inequality and, ultimately, eliminate TB as a public health problem.

What causes TB?

TB is a curable disease caused by a bacterium called *Mycobacterium tuberculosis* (‘*M. tuberculosis*’ or ‘*M.Tb*’). It is spread by one person inhaling the bacterium in droplets coughed or sneezed out by someone with infectious tuberculosis. Not all forms of tuberculosis are infectious. Those with TB in organs other than the lungs are rarely infectious to others, and nor are people with just latent tuberculosis (see below). Some people with pulmonary tuberculosis are infectious, particularly those with bacteria which can be seen on simple microscope examination of the sputum, who are termed ‘smear positive’. The risk of becoming infected depends principally on how long and how intense the exposure to the bacterium is. The risk is greatest in those with prolonged, close household exposure to a person with infectious TB.

What happens after infection?

Once inhaled the bacteria reach the lung and grow slowly over several weeks. The body’s immune system is stimulated, which can be shown by a Mantoux test, a common diagnostic technique. In over 80% of people the immune system kills the bacteria and they are removed from the body. In a small number of cases a defensive barrier is built round the infection but the TB bacteria are not killed and lie dormant. This is called latent tuberculosis; the person is not ill and is not infectious. Sometimes at the time of the initial infection, bacteria get into the blood stream and can be carried to other parts of the body, such as bones, lymph glands or the brain,

[11] Public Health England (2014) Public Health Outcomes Framework 2013 to 2016. Public Health England: London

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before the defensive barrier is built. It is estimated that one third of the world's population, two billion people, have latent tuberculosis.

If the immune system fails to build the defensive barrier, or the barrier fails later, latent tuberculosis can spread within the lung (pulmonary tuberculosis) or develop in the other part(s) of the body it has spread to (extrapulmonary tuberculosis). Only some of those with latent tuberculosis will develop symptoms ('active tuberculosis'). About half the cases of active tuberculosis develop within a few years of the original infection, particularly in children and young adults. The other half of active TB cases arise from reactivation of the latent infection many years later.

Who catches TB?

Anyone can catch TB but those at particular risk are those who have been exposed to TB bacteria, and those who are less able to fight latent infection. They include:

- close contacts of infectious cases;
- those who have lived in, travel to or receive visitors from places where TB is still very common;
- those who live in ethnic minority communities originating from places where TB is very common;
- those with immune systems weakened by HIV infection or other medical problems;
- the very young and the elderly, as their immune systems are less robust;
- those with chronic poor health and nutrition because of lifestyle problems such as homelessness or problem drug or alcohol use;
- those living in poor or crowded housing conditions, including those living in hostels;
- those who have spent time in prison.

What are the symptoms of TB?

Because TB can affect many sites in the body, there can be a wide range of symptoms, some of which are not specific and may delay diagnosis.

Typical symptoms of pulmonary TB include chronic cough, weight loss, intermittent fever, night sweats and coughing blood. TB in parts other than the lungs has symptoms which depend on the site, and may be accompanied by intermittent fever or weight loss. TB is a possible diagnosis to be considered in anyone with intermittent fever, weight loss and other unexplained symptoms. Latent tuberculosis without disease, however, has no symptoms.

How is TB diagnosed?

TB is diagnosed in a number of ways. Tissue samples from biopsies may show changes which suggest TB, as do certain X-ray changes, particularly on chest X-rays. Definite diagnosis is achieved by culturing the TB bacterium from sputum or other samples. This not only confirms the diagnosis, but also shows which of the TB drugs the bacterium is sensitive to. Mantoux test and IGRAs can show if someone has been exposed to TB and may have latent infection. Skin tests use a tiny dose of TB protein injected under the skin. In people who have been exposed to TB this gives a positive reaction, which is seen as a raised, red area. IGRAs involve taking a blood sample, which is processed at a laboratory. Newer rapid molecular diagnostics – nucleic acid amplification tests (NAATs) – that are able to detect small amounts of

genetic material from the mycobacterium by repeatedly amplifying target sequences are also now available.

How is TB treated?

TB is completely curable if the correct drugs are taken for the correct length of time. Before drug treatment for TB nearly half of all persons with active tuberculosis died from it. Several antibiotics need to be taken over a number of months to prevent resistance developing to the TB drugs. The great majority of TB bacteria are sensitive to the antibiotics used (rifampicin, isoniazid, pyrazinamide and ethambutol). A minority of cases, 7.8% in the UK in 2013, are resistant to one of the first line antibiotics[2]. Isoniazid and rifampicin are ineffective in 1% of cases. These cases are said to be of multi-drug resistant TB (MDR TB), which is harder to treat (see Appendix K for details of TB epidemiology).

TB bacteria grow very slowly and divide only occasionally when the antibiotics start to kill them, so treatment usually has to be continued for six months to ensure all active and dormant bacteria are killed and the person with TB is cured. People with pulmonary TB are usually not infectious after two weeks of treatment. Drug-resistant forms of the bacteria require treatment for longer than six months. MDR TB is particularly serious, requiring significantly prolonged (up to 24 months) treatment, with the infectious period lasting much longer.

In latent tuberculosis there are many thousand times fewer TB bacteria than in active tuberculosis. Treatment with a single drug (isoniazid) for six months, or two drugs (isoniazid and rifampicin) for a shorter time, is sufficient to kill most or all of the dormant bacteria, reducing the risk that the person will develop active tuberculosis later in their life.

Following TB treatment, the disease can return (relapse) in a small number of people, because not all bacteria have been killed. This is obviously much more likely if the course of treatment has been interrupted, not completed or otherwise not followed. However, it is also possible to catch TB a second time, unlike some other infectious diseases.

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1.2 Epidemiology of TB in England and Wales [2011, updated 2015]

Up-to-date epidemiological information, including reports of notifications and enhanced surveillance, is available from Public Health England (https://www.gov.uk/government/organisations/public-health-england).

Historical trends

The TB notification system, implemented in 1913, showed that recorded TB rates peaked in England and Wales in the early part of the twentieth century, when 300 new cases per 100,000 people were reported every year. Since then, until the mid 1980s at least, the incidence of tuberculosis has been falling: in 1987 there were only 10 new cases per 100,000 people.

[2] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London

Geographical variations in incidence

There are marked differences in the incidence of tuberculosis in different parts of the UK, with most new cases occurring in cities. For example, there were 35.5 new cases per year per 100,000 population in London in 2013, as compared to less than 4 in the south west of England[3]. There are also substantial variations in incidence of TB within cities, with as much as a thirtyfold difference between different London boroughs.

Variations in incidence by ethnicity and place of birth

Risk of TB is significantly higher in people from minority ethnic groups and in people born outside of the UK, as is evident in Table 1. The majority of cases in people born abroad occur after they have lived in the UK for several years.

Table 1: Tuberculosis rates in the UK by ethnicity and place of birth, 2013[4]

Ethnicity	TB cases per 100,000 population
Black African, UK-born	31
Black African, non-UK-born	170
Pakistani, UK-born	38
Pakistani, non-UK-born	286
Indian, UK-born	30
Indian, non-UK-born	220
White, UK-born	3
White, non-UK born	11

[3] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London
[4] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London

1.3 GDG and SDG membership and ICG technical team

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1.4 Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Committee is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendation wording in guideline updates

NICE began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2006], [2011] and [2012] (see 'Update information' box below for details about how recommendations are labelled). In particular, for recommendations labelled [2006] and [2012], the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Update information

Our first guideline on TB was published in 2006. This was updated in 2011. This guideline is an update of tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (published March 2011) and will replace it. It also incorporates and adapts the guideline on identifying and managing TB in hard-to-reach groups published in March 2012.

It has not been possible to update all sections and recommendations in this update of the guideline. This means some of the recommendations that have not been

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reviewed may not reflect current practice. Areas for review and update were identified, prioritised and agreed through the scoping process.

Areas that have not been reviewed in this update may be addressed 2 years after publication, when NICE next considers updating this guideline. NICE may undertake a more rapid update of discrete areas of the guideline if new and relevant evidence is published.

Recommendations in the guideline update have been labelled to show:

- the year each recommendation was written and the year(s) of any updates
- which parts of the guideline are open for stakeholder comment at consultation.

The sections below explain this labelling in more detail.

Recommendations open for comment (with an evidence review)

New recommendations have been added for the diagnosis, treatment, monitoring and support of people with TB, as well as the prevention of the transmission of infection. New recommendations have also been added on organising TB services.

You are invited to comment on the new and updated recommendations in this guideline. These are marked as:

- [new 2015] if the evidence has been reviewed and the recommendation has been added or updated
- [2015] if the evidence has been reviewed as part of the update but no change has been made to the recommended action.

Recommendations not open for comment (no evidence review)

Recommendations where the evidence has not been reviewed for the 2015 update are not open for comment. These recommendations end [2006], [2006, amended 2011], [2011] or [2012].

Recommendations ending [2006, amended 2011, amended 2015], [2006, 2012, amended 2015], [2011, amended 2015] or [2012, amended 2015], the evidence has not been reviewed but changes have been made to the recommendation wording that change the meaning (for example, because of equalities duties or a change in the availability of medicines, or incorporated guidance has been updated). We will not be able to accept comments on these recommendations.

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1.5 Recommendations

1. Offer Mantoux testing to diagnose latent TB in adults aged 18 to 65 who are:
   - household contacts of a person with pulmonary TB
   - non-household contacts (other close contacts for example, in workplaces) of people with pulmonary TB.

   An induration of 5 mm or larger, regardless of BCG history, is considered a positive test result. **[2011, amended 2015]**
2. Consider interferon-gamma testing for adults aged 18 to 65 whose Mantoux test shows positive results (5 mm or larger, regardless of BCG history), or in people for whom Mantoux testing may be less reliable, for example, BCG-vaccinated people. [2011, amended 2015]
3. If Mantoux test is inconclusive, refer the person to a TB specialist. [2011]
4. Only consider using interferon-gamma release assays in children and young people if Mantoux testing is not available or is impractical (for example, situations in which large numbers need to be tested). [new 2015]
5. If a neonate has been in close contact with people with pulmonary TB and has not had at least 2 weeks of anti-TB treatment:
   - Assess for active TB.
   - Start isoniazid for 3 months.
   - Carry out a Mantoux test after 3 months of treatment.
   - If the Mantoux test is positive (5 mm or larger, regardless of BCG history), reassess for active TB (see section 1.3.1). If this assessment for active TB is negative, continue isoniazid for a total of 6 months.
   - If the Mantoux test is negative, consider an interferon-gamma release assay:
     - if both are negative then stop isoniazid and give a BCG vaccination
     - if the interferon-gamma release assay is positive, reassess for active TB; if the test for active TB is negative, continue isoniazid treatment for a total of 6 months. **[new 2015]**
6. Treat children aged between 4 weeks and 2 years and in close contact with people with pulmonary TB as follows:
   - Start isoniazid and carry out a Mantoux test.
   - If the Mantoux test is positive (5 mm or larger, regardless of BCG history), assess for active TB.
   - If active TB is ruled out, give full treatment for latent TB infection.

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- If the Mantoux test is negative, continue isoniazid for 6 weeks, then repeat the Mantoux test and consider an interferon-gamma release assay:
  - if the repeat tests are negative, isoniazid may be stopped; give a BCG vaccination if the child has not already had one
  - if either repeat test is positive, assess for active TB and if the assessment is negative, complete treatment for latent TB. **[new 2015]**

7. Refer children younger than 2 years and in close contact with people with smear-negative pulmonary TB to a specialist to determine what testing strategy for latent TB would be most appropriate. [new 2015]
8. Offer Mantoux testing for latent TB in people aged between 2 and 17 years who are:
   - household contacts of a person with pulmonary TB
   - non-household contacts (other close contacts, for example, in workplaces and schools) of people with pulmonary TB. **[new 2015]**
9. If the Mantoux test is positive (5 mm or larger, regardless of BCG history) in people aged between 2 and 17 years:
   - assess for active TB, and
   - consider treating them for latent TB infection. **[new 2015]**
10. If the initial Mantoux test is negative but the child is a contact of a person with sputum-smear-positive disease, offer an interferon-gamma test after 6 weeks and repeat the Mantoux test to increase the sensitivity (to reduce false negative results). [new 2015]
11. Assess and manage TB in new entrants from high incidence countries as follows:
    - assess risk of HIV, including HIV prevalence rates in the country of origin, and take this into account in deciding whether to give a BCG vaccination
    - offer testing for latent TB
    - assess for active TB if the test for latent TB is positive
    - offer treatment to people aged 65 years or younger in whom active TB has been excluded but who have a positive Mantoux test inconsistent with their BCG history and a positive interferon-gamma release assay for latent TB infection
    - consider offering BCG for unvaccinated people who are Mantoux negative
    - give 'inform and advise' information to people who do not have active TB and are not being offered BCG or treatment for latent TB infection. **[2006, amended 2011 and 2015]**

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12. Primary care services should support local, community-based and voluntary organisations that work with vulnerable migrants to ensure they:
    - register with a primary care provider
    - know how to use NHS services (emergency or primary care). **[2012]**
13. Healthcare professionals, including primary care staff, responsible for screening new entrants should screen all vulnerable migrants who have not previously been checked (see section 1.2.1). This is regardless of when they arrived in England. People born in countries with an incidence of more than 150 per 100,000 per year should be made a priority for latent TB screening when they arrive here. [2012]
14. Offer Mantoux testing as the initial diagnostic test for latent TB infection in people who have recently arrived from a high-incidence country. If the Mantoux test is positive (5 mm or larger, regardless of BCG history):
    - assess for active TB, and
    - consider treating them for latent TB infection.

    If this is unavailable offer an interferon-gamma release assay test. **[new 2015]**
15. If latent TB is suspected in children and young people who are immunocompromised, refer to a TB specialist. [2015]
16. In adults who are anticipated to be or are currently immunocompromised, do a risk assessment to establish whether testing should be offered, taking into account their:
    - risk of progression to active TB based on how severely they are immunocompromised and for how long they have been immunocompromised
    - risk factors for TB infection, such as country of birth or recent contact with an index case with suspected infectious or confirmed pulmonary or laryngeal TB. **[new 2015]**
17. For adults who are severely immunocompromised, such as those with HIV and CD4 counts of fewer than 200 cells/mm^3, or after solid organ or allogeneic stem cell transplant, offer an interferon-gamma release assay and a concurrent Mantoux test. If either test is positive (for Mantoux, this is an induration of 5 mm or larger, regardless of BCG history):
    - assess for active TB, and
    - consider treating them for latent TB infection. **[new 2015]**
18. For other adults who are immunocompromised, consider an interferon-gamma release assay alone or an interferon-gamma release assay with a concurrent Mantoux test. If either test is positive (for Mantoux, this is an induration of 5 mm or larger, regardless of BCG history):
    - assess for active TB, and

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- consider treating them for latent TB infection. **[new 2015]**

19. In an outbreak situation when large numbers of people may need to be screened, consider a single interferon-gamma release assay for people aged 18–65 years. [2011, amended 2015]

20. Offer a Mantoux test to new NHS employees who will be in contact with patients or clinical materials, if the employees:

    - are not new entrants from high-incidence countries and
    - have not had BCG vaccination (for example, they are without a BCG scar, other documentation or a reliable history). [2011]

21. Offer Mantoux testing as the initial diagnostic test for latent TB infection in new NHS employees who have recently arrived from a high-incidence country. If the Mantoux test is positive (5 mm or larger, regardless of BCG history):

    - assess for active TB, and
    - consider treating them for latent TB infection.

    If this is unavailable offer an interferon-gamma release assay test. [new 2015]

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22. Offer an interferon-gamma release assay test to new NHS employees who have had contact with patients in settings where TB is highly prevalent. [2011, amended 2015]

23. Healthcare workers who are immunocompromised should be screened in the same way as other people who are immunocompromised. [2011]

24. Offer adults aged 18–65 years from under-served groups a single interferon-gamma release assay. [2011, amended 2015]

25. Substance misuse services with access to an interferon-gamma release assay should provide testing for adults aged 18–65 years if they:

    - live in a high incidence area
    - are likely to be involved with substance misuse services or other support services on a regular basis (for example, for opioid substitution therapy), when support should be available for directly observed preventive therapy. [2012, amended 2015]

26. In high incidence areas (and at prisons that receive prisoners from high incidence areas), prison health services should offer an interferon-gamma release assay test for TB to inmates younger than 65 years who are in regular contact with substance misuse services or other support services. This is provided arrangements have been made for this support to continue after release. [2012, amended 2015]

27. Substance misuse services and prison health services should incorporate interferon-gamma release assay testing with screening for hepatitis B and C, and HIV testing. They should refer prisoners and people who misuse substances with positive interferon-gamma release assay tests to local multidisciplinary TB teams for further clinical investigations. For prisoners, these

investigations should be done in the prison if practically possible. [2012, amended 2015]

28. If TB is a possibility, microbiology staff should consider carrying out TB culture on samples, even if it is not requested. [2006, amended 2015]

29. If there are clinical signs and symptoms consistent with a diagnosis of TB, start treatment without waiting for culture results. [2006]

30. Consider completing the standard recommended regimen, even if subsequent culture results are negative. [2006, amended 2015]

31. Take a posterior-anterior chest X-ray; do further diagnostic investigations (as detailed below and summarised in table 1) if chest X-ray appearances suggest TB. [2015] Update 2015

32. Send multiple respiratory samples (3 deep cough sputum samples, preferably with 1 early morning sample) for TB microscopy and culture. [2015]

- This should be before starting treatment if possible, or, failing that, within 7 days of starting treatment in people with life-threatening disease. **[2006, amended 2015]**
- Obtain spontaneously-produced, deep cough sputum samples if possible, otherwise use:
  - 3 gastric lavages or 3 inductions of sputum in children and young people **[new 2015]**, or Update 2015
  - induction of sputum or bronchoscopy and lavage in adults. **[2006, amended 2015]**
- Laboratory practices should be in accordance with Public Health England's Standards for Microbiology Investigations. **[new 2015]** Update 2015

33. Send samples for TB culture from autopsy samples if pulmonary TB is a possibility. [2006]

34. A TB specialist should request rapid diagnostic nucleic acid amplification tests for the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*) on primary specimens (listed in table 1) if there is clinical suspicion of TB disease, and:

- the person has HIV, or
- rapid information about mycobacterial species would alter the person's care, or
- the need for a large contact-tracing initiative is being explored. [new 2015]

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35. In children and young people aged 15 years or younger with suspected pulmonary TB, offer rapid diagnostic nucleic acid amplification tests for the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*). Usually only 1 nucleic acid amplification test will be necessary per specimen type (for example, spontaneous sputum, induced sputum or gastric lavage). (Listed in table 1). [new 2015]

36. In young people aged 16–18 years use the same criteria as in adults to decide whether to request rapid diagnostic nucleic acid amplification tests (see table 1). [new 2015]

37. Either a paediatrician with experience and training in the treatment of TB or a general paediatrician with advice from a specialised clinician should investigate and manage TB in children and young people. [new 2015]

38. An expert in paediatric TB may request interferon gamma release assays and tuberculin skin tests. Interpret these together with other diagnostic tools (such as history taking, clinical examination and imaging). [new 2015]

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39. Discuss the advantages and disadvantages of both biopsy and needle aspiration with the patient, with the aim of obtaining adequate material for diagnosis. [2006]

40. Do not place part or all of any of the samples in formalin (or other fixative agent) when sending for TB culture. [2006, amended 2015]

41. Think about a diagnosis of extrapulmonary TB even if rapid diagnostic tests in, for example, cerebrospinal fluid, pleural fluid or ascitic fluid are negative. [new 2015]

42. Offer all patients presenting with extrapulmonary TB a chest posterior-anterior X-ray and, if possible, culture of a spontaneously-produced respiratory sample to exclude or confirm coexisting pulmonary TB. Also, consider site-specific tests as described below to exclude or confirm additional sites of TB. [new 2015]

43. Refer to an expert for sites not listed here, including TB of the eye and other rare sites of disease. [new 2015]

Pleural TB

44. Use the site-specific investigations listed in table 2 to diagnose and assess pleural TB.

Table 2 Site-specific investigations for pleural TB

[new 2015]

Central nervous system TB

45. Use the site-specific investigations listed in table 3 to diagnose and assess central nervous system TB.

Table 3 Site-specific investigations for central nervous system TB

[new 2015]

46. Offer treatment for TB meningitis if clinical signs and other laboratory findings are consistent with the diagnosis, even if a rapid diagnostic test is negative. [new 2015]

Lymph node TB

47. Use the site-specific investigations listed in table 4 to diagnose and assess lymph node TB.

Table 4 Site-specific investigations for lymph node TB

[new 2015]:

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Pericardial TB

48. Use the site-specific investigations listed in table 5 to diagnose and assess pericardial TB.

Table 5 Site-specific investigations for pericardial TB

[new 2015]

Gastrointestinal TB

49. Use the site-specific investigations listed in table 6 to diagnose and assess gastrointestinal TB.

Table 6 Site-specific investigations for gastrointestinal TB

[new 2015]

Genitourinary TB

50. Use the site-specific investigations listed in table 7 to diagnose and assess genitourinary TB.

Table 7 Site-specific investigations for genitourinary TB

[new 2015]

Bone and joint TB

51. Use the site-specific investigations listed in table 8 to diagnose and assess bone and joint TB.

Table 8 Site-specific investigations for bone and joint TB

[new 2015]

Disseminated TB

52. Use the site-specific investigations listed in table 9 to diagnose and assess disseminated TB.

Table 9 Site-specific investigations for disseminated TB

[new 2015]

Skin TB

53. Use the site-specific investigations listed in table 10 to diagnose and assess skin TB.

Table 10: Site-specific investigations for skin TB

[2015]

Localised tuberculous abscess

54. Use the site-specific investigations listed in table 11 to diagnose and assess TB in a localised, tuberculous abscess at a site other than a lymph node.

Table 11: Site-specific investigations for localised tuberculous abscess

[2015]

55. Use fixed-dose combination tablets as part of any TB treatment regimen. [2006]

56. Do not offer anti-TB treatment dosing regimens of fewer than 3 times per week. [2006, amended 2015]

57. Offer a daily dosing schedule to people with active pulmonary TB. [2006, amended 2015]

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58. Consider a daily dosing schedule as first choice in people with active extrapulmonary TB. [2006, amended 2015]

59. Consider 3 times weekly dosing for people with active TB only if:

    - risk assessment identifies a need for directly observed therapy and enhanced case management and
    - daily directly observed therapy is not possible. **[2006, amended 2015]**

60. Once a diagnosis of active TB is made:

    - the clinician responsible for care should refer the person with TB to a clinician with training in, and experience of, the specialised care of people with TB
    - the TB service should include specialised nurses and health visitors
    - TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised clinician.

    If these arrangements are not possible, seek advice from more specialised colleagues throughout the treatment period. **[2015]**

61. For people with active TB without central nervous system involvement, offer:

    - isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, then
    - isoniazid and rifampicin for a further 4 months.

    Modify the treatment regimen according to drug susceptibility testing. **[2015]**

62. For people with active TB of the central nervous system, offer:

    - isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, then
    - isoniazid and rifampicin for a further 10 months.

    Modify the treatment regimen according to drug susceptibility testing. **[2015]**

63. Test people with active spinal TB who have neurological signs or symptoms for central nervous system involvement. Manage direct spinal cord involvement (for example, a spinal cord tuberculoma) as TB of the central nervous system. [2015]

64. For people with active spinal TB without central nervous system involvement, do not extend treatment beyond 6 months for residual effects (for example, persistent bending of the spine or vertebral loss). [2015]

65. Test people with disseminated (including miliary) TB for central nervous system involvement. If there is evidence of central nervous system involvement, treat as for TB of the central nervous system. [2015]

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66. Treat active peripheral lymph node TB in people who have had an affected gland surgically removed with the standard recommended regimen. [new 2015]

67. For people with active TB of the lymph nodes, do not routinely extend treatment beyond 6 months for newly enlarged lymph nodes or sinus formation, or for residual enlargement of the lymph nodes or sinuses. [new 2015]

Central nervous system TB

68. At the start of an anti-TB treatment regimen, offer people with active TB of the central nervous system dexamethasone or prednisolone, initially at a high dose with gradual withdrawal over 4–8 weeks. An example of a suitable regimen is listed in table 12.

Table 12 Example of suitable corticosteroid regimen for adults

69. At the start of an anti-TB treatment regimen, offer children and young people with active TB of the central nervous system dexamethasone or prednisolone. This should initially be at a high dose with gradual withdrawal over 4–8 weeks. An example of a suitable regimen is oral prednisolone, starting at a dose of 4 mg/kg of body weight/day. [new 2015]

Pericardial TB

70. In adults with active pericardial TB, offer oral prednisolone at a starting dose of 60 mg/day, gradually withdrawing it 2–3 weeks after starting treatment. [2015]

71. In children and young people with active pericardial TB, offer oral prednisolone at a starting dose of 1 mg/kg of body weight/day (maximum 40 mg/day), gradually withdrawing it 2–3 weeks after starting treatment. [2015]

72. If surgery is indicated, the surgeon should fully explain what is involved to the person, either with or after consulting a TB specialist. Discuss the possible benefits and risks with the person and their family members or carers, as appropriate, so that they can make an informed decision. [new 2015]

Central nervous system TB

73. Consider surgery as a therapeutic intervention in people with TB of the central nervous system only if there is evidence of raised intracranial pressure. [new 2015]

Spinal TB

74. Do not routinely perform surgery in people with spinal TB to eradicate the disease. [new 2015]

75. Consider surgery in people with spinal TB if there is spinal instability or evidence of spinal cord compression. [new 2015]

Drug resistant TB

76. Consider surgery as a therapeutic intervention in people with potentially resectable multidrug-resistant disease if:

- optimal medical therapy under direct observation has not worked, or

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- medical therapy is likely to fail because of extensively drug-resistant TB. **[new 2015]**

77. If the person has a comorbidity or coexisting condition such as:
    - HIV, or
    - severe liver disease, for example, Child-Pugh level B or C, or
    - stage 4 or 5 chronic kidney disease (a glomerular filtration rate of <30 ml/minute/1.73m^2), or
    - diabetes, or
    - eye disease or impaired vision, or
    - pregnancy or breastfeeding, or
    - a history of alcohol or substance misuse

    work with a specialist multidisciplinary team with experience of managing TB and the comorbidity or coexisting condition. **[new 2015]**
78. For people with HIV and active TB without central nervous system involvement, do not routinely extend treatment beyond 6 months. [new 2015]
79. For people with HIV and active TB with central nervous system involvement, do not routinely extend treatment beyond 12 months. [new 2015]
80. Take into account drug-to-drug interactions when co-prescribing antiretroviral and anti-TB drugs. [new 2015]
81. In people who have experienced a treatment interruption because of drug-induced hepatotoxicity:
    - investigate other causes of acute liver reactions
    - wait until aspartate or alanine transaminase levels fall below twice the upper limit of normal, bilirubin levels return to the normal range and hepatotoxic symptoms have resolved, then
    - sequentially reintroduce each of the anti-TB drugs over a period of no more than 10 days, starting with ethambutol and either isoniazid or rifampicin. **[new 2015]**
82. In people with severe or highly infectious TB who need to interrupt standard therapy because of a reaction, consider continuing treatment with:
    - for hepatotoxicity, a combination of at least 2 anti-TB drugs of low hepatotoxicity (such as ethambutol and streptomycin, with or without a quinolone, such as levofloxacin or moxifloxacin) and monitor with a liver specialist for further reactions
    - for a cutaneous reaction, a combination of at least 2 anti-TB drugs with a low risk of cutaneous reactions (such as ethambutol and streptomycin) and monitor with a dermatologist for further reactions. [new 2015]

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83. If another reaction of a similar or greater severity occurs because of reintroducing a particular drug, exclude that drug from future regimens and consider extending the total regimen accordingly. [new 2015]

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84. Follow-up clinic visits should not be conducted routinely after treatment completion. [2006]

85. Tell patients to watch for symptoms of relapse and how to contact the TB service rapidly through primary care or a TB clinic. Key workers should ensure that patients at increased risk of relapse are particularly well informed about symptoms. [2006]

86. Patients who have had drug-resistant TB should be considered for follow-up for 12 months after completing treatment. Patients who have had multidrug-resistant TB should be considered for prolonged follow-up. [2006]

87. As soon as possible, explore options to reduce the psychosocial impact of prolonged isolation. For example, through providing free access to Internet, telephone and television, and accompanied walks in the open air. [new 2015]

88. For people with clinically suspected TB, a TB specialist should request rapid diagnostic nucleic acid amplification tests for rifampicin resistance on primary specimens if a risk assessment for multidrug resistance identifies any of the following risk factors:

- history of previous TB drug treatment, particularly if there was known to be poor adherence to that treatment
- contact with a known case of multidrug-resistant TB
- birth or residence in a country in which the World Health Organization reports that a high proportion (5% or more) of new TB cases are multidrug-resistant. **[new 2015]**

89. If the rapid diagnostic nucleic acid amplification test for rifampicin resistance is positive:

- start infection control measures and continue until pulmonary disease has been excluded
- manage treatment along with a multidisciplinary team with experience of managing multidrug-resistant TB
- offer a treatment regimen involving at least 6 drugs to which the mycobacterium is likely to be sensitive
- test for resistance to second-line drugs. **[new 2015]**

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90. If the rapid diagnostic nucleic acid amplification test for the *M. tuberculosis* complex is positive but rifampicin resistance is not detected, treat as drug-susceptible TB with the standard regimen. [new 2015]

91. If the rapid diagnostic nucleic acid amplification test for the *M. tuberculosis* complex is negative in a person at high risk of multidrug-resistant TB:

- obtain further specimens for nucleic acid amplification testing and culture, if possible

- use rapid rifampicin resistance detection on cultures that become positive for the *M. tuberculosis* complex
- consider waiting for the results of further tests before starting treatment if the person is well
- if urgent treatment is necessary, consider managing as multidrug-resistant TB until sensitivity results are available. **[new 2015]**

92. When definitive phenotypic susceptibility results are available, modify treatment as needed. [new 2015]

93. Consider more intensive clinical follow-up for people with multidrug-resistant TB. This includes those having directly observed therapy throughout treatment because of the complexity of treatment and risk of adverse events. [new 2015]

94. Discuss the options for organising care for people with multidrug-resistant TB with clinicians who specialise in this. Seek the patient's views and take them into account, and consider shared care. [2006]

95. For people with TB, without central nervous system involvement, that is resistant to just 1 drug consider the treatments in table 20.

96. For people with drug-resistant TB and central nervous system involvement, involve a TB specialist with experience in managing drug-resistant TB in decisions about the most appropriate regimen and the duration of treatment. [new 2015]

97. Ensure healthcare settings can promptly identify people with suspected infectious or confirmed pulmonary TB before or at presentation. Ensure people working in the settings follow the recommendations about testing and treatments. [new 2015]

98. Put patients with suspected infectious or confirmed pulmonary TB who will remain in a hospital setting (including emergency, outpatients or inpatient care) in a single room. If this is not possible, keep the person's waiting times to a minimum. This may involve prioritising their care above that of other patients. [new 2015]

99. Minimise the number and duration of visits a person with TB makes to an outpatient department while they are still infectious. To minimise the risk of infection, people with infectious TB should be seen at times or in places away from other patients. [new 2015]

100. In hospital settings, risk assess people with suspected infectious or confirmed pulmonary TB for multidrug-resistant TB. Care for those deemed to be at low risk in a single room, as a minimum. For those deemed to be at high risk:
    - provide care in a negative pressure room, and
    - have specimens sent for rapid diagnostic tests, such as nucleic acid amplification tests. **[new 2015]**

101. Unless there is a clear clinical or public health need, such as homelessness, people with suspected infectious or confirmed pulmonary TB should not be admitted to hospital for diagnostic tests or for care. [2006, amended 2015]

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102. Do not admit people with suspected infectious or confirmed pulmonary TB to a ward containing immunocompromised patients, such as transplant recipients, people with HIV and those on anti-tumour necrosis factor alpha or other biologics, unless they can be cared for in a negative-pressure room on the same ward. [new 2015]

103. Assess any visitors to a child with suspected active TB in hospital for symptoms of infectious TB, and keep them separate from other patients until they have been excluded as a source of infection. [new 2015]

104. In people who may have TB, only carry out aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment in an appropriately engineered and ventilated area (ideally a negative pressure room). [new 2015]

105. Ask inpatients with suspected infectious or confirmed pulmonary TB (with explanation) to wear a surgical mask in the hospital whenever they leave their room, until they have had at least 2 weeks of treatment. [2015]

106. Offer patients advice on simple respiratory hygiene measures. [new 2015]

107. In non-healthcare settings catering for large numbers of people and populations at high risk of TB (such as detention settings, residential hostels and day centres):

- promote simple respiratory hygiene
- ensure awareness of symptoms of potentially infectious TB to enable prompt healthcare referral
- seek advice from the local public health team and the local authority on accommodating people with TB
- ensure adequate ventilation. **[new 2015]**

108. If people with suspected or known infectious multidrug-resistant TB are admitted to hospital, admit them to a negative-pressure room. If none is available locally, transfer them to a hospital that has these facilities and a clinician experienced in managing complex drug-resistant cases. Carry out care in a negative-pressure room for people with:

- suspected multidrug-resistant TB, until non-resistance is confirmed
- confirmed multidrug-resistant TB, until they have 3 negative smears at weekly intervals and are ideally culture negative. **[new 2015]**

109. For people with confirmed multidrug-resistant TB whose symptoms have improved and who are unable to produce sputum, discharge decisions should be taken by the multidisciplinary team and the health protection team. [new 2015]

110. Staff and visitors should wear FFP3 masks during contact with a patient with suspected or known multidrug-resistant TB while the patient is thought to be infectious. [2015]

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111. Before deciding to discharge a patient with suspected or known multidrug-resistant TB from hospital, agree with the patient and carers secure arrangements for supervising and administering all anti-TB therapy. [2015]

112. Discuss the decision to discharge a patient with suspected or known multidrug-resistant TB with:

- the infection control team
- the local microbiologist
- the local TB service and
- the health protection team. **[2015]**

113. Ensure negative-pressure rooms used for infection control in multidrug-resistant TB meet the standards of the Interdepartmental Working Group on Tuberculosis, and are clearly identified for staff, for example by a standard sign. Keep such signs up to date. [2015]

Healthcare settings

114. Care for people with a continuing clinical or public health need for admission with pulmonary TB in a single room (as a minimum) until they have completed 2 weeks of the standard treatment regimen (see section 1.3.2) if they:

- are unlikely to be rifampicin resistant (that is, do not have risk factors for multidrug-resistant TB, or
- have negative rifampicin resistance on nucleic acid amplification test or culture. **[new 2015]**

115. Consider de-escalating isolation after 2 weeks of treatments, taking into account the risks and benefits, if:

- the person is showing tolerance to the prescribed treatment
- there is agreement to adhere to treatment
- there is resolution of cough
- there is definite clinical improvement on treatment; for example, remaining afebrile for a week
- there are not immunocompromised people, such as transplant recipients, people with HIV and those on anti-tumour necrosis factor alpha or other biologics, in the same accommodation
- the person's initial smear grade was not high; for example, 2 or less
- there is not extensive pulmonary involvement, including cavitation
- there is no laryngeal TB. **[new 2015]**

116. Consider discharging from hospital people:

- who do not have a continuing clinical or public health need for admission with pulmonary TB, and

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- who are unlikely to be rifampicin resistant (that is, do not have risk factors for multidrug-resistant TB), or
- who have negative rifampicin resistance on nucleic acid amplification test or culture.

If discharged, congregate settings should be avoided for the first 2 weeks of their treatment. [new 2015]

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Non-healthcare settings

117. In prisons or immigration removal centres, everyone with X-ray changes indicative of active TB, as well as those with symptoms who are awaiting X-ray, should be isolated in an adequately ventilated individual room or cell. Prisoners and detainees should be retained on medical hold until they have:
    - proven smear negative and had a posterior-anterior X-ray that does not suggest active TB, or
    - had a negative risk assessment for multidrug-resistant TB and completed 2 weeks of the standard treatment regimen. **[2012, amended 2015]**

Multidrug-resistant TB

118. Consider earlier discharge for people with confirmed multidrug-resistant TB, if there are suitable facilities for home isolation and the person will adhere to the care plan. [new 2015]

119. Be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who:
    - are HIV positive
    - have excessive alcohol intake
    - are injecting drug users
    - have had solid organ transplantation
    - have a haematological malignancy
    - have had a jejunoileal bypass
    - have diabetes
    - have chronic renal failure or receive haemodialysis
    - have had a gastrectomy
    - are having anti-tumour necrosis factor-alpha treatment or other biologic agents
    - have silicosis.

    People in these groups who do not have treatment for latent TB, as specified in recommendations 120 to 127, for any reason should be advised of the risks and symptoms of TB (on the basis of an individual risk assessment), usually in a standard letter of the type referred to as 'Inform and advise' information, and have posterior-anterior chest X-rays 3 and 12 months later. [new 2015]

120. For people, including those with HIV, aged younger than 65 years with evidence of latent TB who have been in close contact with

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people who have suspected infectious or confirmed active pulmonary or laryngeal drug-sensitive TB offer either of the following drug treatments:

- 3 months of isoniazid and rifampicin, or
- 6 months of isoniazid. [new 2015]

121. For adults between the ages of 35 and 65 years, offer drug treatments only if hepatotoxicity is not a concern. [new 2015]

122. Base the choice of regimen on the person's clinical circumstances. Offer:

- 3 months of isoniazid and rifampicin if hepatotoxicity is a concern; this would include both liver function (including transaminase) tests and assessment of risk factors
- 6 months of isoniazid if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant. [new 2015]

123. Clearly explain the risks and potential benefits of each treatment regimen. In discussion with the person, select a suitable regimen if they wish to proceed with preventive treatment. [new 2015]

124. Offer testing for HIV and hepatitis B and C before starting treatment for latent TB. For recommendations on hepatitis B and C, see NICE guidelines on Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults. For recommendations on HIV, see NICE guidelines on Increasing the uptake of HIV testing among black Africans in England and Increasing the uptake of HIV testing among men who have sex with men. [new 2015]

125. If a person also has severe liver disease, for example, Child-Pugh level B or C, work with a specialist multidisciplinary team with experience of managing TB and liver disease. [new 2015]

126. Manage treatment with caution, ensuring careful monitoring of liver function, in:

- people with non-severe liver disease
- people with abnormal liver function (including abnormal transaminase levels) before starting treatment for latent TB infection
- people who misuse alcohol or drugs. [new 2015]

127. Ensure people having treatment for latent TB who also have social risk factors, such as misusing alcohol or drugs or being homeless, are linked to support services. They should also have an assessment of social needs and stability, including potential barriers to adherence or treatment completion. [new 2015]

128. To improve the uptake of BCG vaccination, identify eligible groups (in line with the Department of Health's Green Book) opportunistically through several routes, for example:

- new registrations in primary care and with antenatal services

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- people entering education, including university
- links with statutory and voluntary groups working with new entrants and looked-after children and young people
- during contact investigations. **[new 2015]**

129. When BCG is being recommended, discuss the benefits and risks of vaccination or remaining unvaccinated with the person (or, if a child, with the parents), so that they can make an informed decision. Tailor this discussion to the person, use appropriate language, and take into account cultural sensitivities and stigma. [2006]

130. If people identified for BCG vaccination through occupational health, contact tracing or new entrant screening are also considered to be at increased risk of being HIV positive, offer them HIV testing before BCG vaccination. [2006]

131. Discuss neonatal BCG vaccination for any baby at increased risk of TB with the parents or legal guardian. [2006]

132. Primary care organisations with a high incidence of TB should consider vaccinating all neonates soon after birth. [2006]

133. In areas with a low incidence of TB (see Public Health England's tuberculosis rate bands), primary care organisations should offer BCG vaccination to selected neonates who:

- were born in an area with a high incidence of TB, or
- have 1 or more parents or grandparents who were born in a high-incidence country, or
- have a family history of TB in the past 5 years. **[2006]**

134. Routine BCG vaccination is not recommended for children aged 10–14 years.

- Healthcare professionals should opportunistically identify unvaccinated children older than 4 weeks and younger than 16 years at increased risk of TB who would have qualified for neonatal BCG and provide Mantoux testing and BCG vaccination (if Mantoux negative).
- This opportunistic vaccination should be in line with the Green Book. **[2006, amended 2015]**

135. Mantoux testing should not be done routinely before BCG vaccination in children younger than 6 years unless they have a history of residence or prolonged stay (more than 1 month) in a country with a high incidence of TB. [2006]

136. Offer BCG vaccination to new entrants who are Mantoux-negative who:

- are from high-incidence countries, and
- are previously unvaccinated (that is, without adequate documentation or a BCG scar), and
- are aged:
  - younger than 16 years, or

- 16–35 years from sub-Saharan Africa or a country with a TB incidence of 500 per 100,000 or more. **[2006]**

137. Offer BCG vaccination to healthcare workers and other NHS employees who have contact with patients or clinical specimens, irrespective of age, who:
    - are previously unvaccinated (that is, without adequate documentation or a BCG scar), and
    - are Mantoux (or interferon-gamma release assay) negative. **[2006, amended 2015]**
138. Offer BCG vaccination to Mantoux-negative contacts of people with pulmonary TB (see section 1.6.1 for details of contact tracing) if they have not been vaccinated previously (that is, there is no adequate documentation or a BCG scar) and are:
    - aged 35 years or younger, or
    - aged 36 years and older and a healthcare or laboratory worker who has contact with patients or clinical materials. **[2006, amended 2015]**
139. Offer BCG vaccination to previously unvaccinated, Mantoux-negative people aged 35 years or younger in the following groups at increased risk of exposure to TB, in accordance with the Green Book:
    - veterinary and other staff such as abattoir workers who handle animal species known to be susceptible to TB, such as simians
    - prison staff working directly with prisoners
    - staff of care homes for older people
    - staff of hostels for people who are homeless and facilities accommodating refugees and asylum seekers
    - people going to live or work with local people for more than 1 month in a high-incidence country. **[2006]**
140. To improve the uptake of BCG vaccination, identify eligible groups (in line with the Department of Health's Green Book) opportunistically through several routes, for example:
    - new registrations in primary care and with antenatal services
    - people entering education, including university
    - links with statutory and voluntary groups working with new entrants and looked-after children and young people
    - during contact investigations. **[new 2015]**
141. When BCG is being recommended, discuss the benefits and risks of vaccination or remaining unvaccinated with the person (or, if a child, with the parents), so that they can make an informed decision. Tailor this discussion to the person, use appropriate language, and take into account cultural sensitivities and stigma. [2006]

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142. If people identified for BCG vaccination through occupational health, contact tracing or new entrant screening are also considered to be at increased risk of being HIV positive, offer them HIV testing before BCG vaccination. [2006]

BCG vaccination in neonates (0–4 weeks)

143. Identify babies eligible for vaccination (in line with the Green Book) before birth, ideally through antenatal services. [new 2015]

144. Preferably vaccinate babies at increased risk of TB before discharge from hospital or before handover from midwifery to primary care. Otherwise, vaccinate as soon as possible afterwards, for example, at the 6-week postnatal check. [new 2015]

145. Incorporate computer reminders into maternity service (obstetrics) IT systems for staff, to identify and offer BCG vaccination to babies eligible for vaccination. [new 2015]

146. Provide education and training for postnatal ward staff, midwives, health visitors and other clinicians on identifying babies eligible for vaccination, local service information and providing BCG vaccination, including:

- case definition for at-risk groups to be offered vaccination
- information about the local BCG vaccination policy that can be given verbally, in writing or in any other appropriate format (see sections 1.1.1 and 1.1.2) to parents and carers at the routine examination of the baby before discharge
- local service information about BCG vaccination, such as pre-discharge availability of neonatal vaccination, local BCG clinics and referral for BCG vaccination if this is not available in maternity services
- administration of BCG vaccination and contraindications. **[new 2015]**

Encouraging uptake among infants, older children and new entrants

147. Deliver the following interventions in primary care settings to improve uptake of BCG vaccination in people from eligible groups (as outlined in the Green Book):

- education and support for practice staff, including:
  - raising awareness of relevant guidelines and case definition for at-risk groups
  - promoting BCG and TB testing in eligible groups
- incorporating reminders for staff (prompts about eligibility for BCG) on practice computers (for example, embedded in medical records)
- consider financial incentives for practices for identifying eligible groups for BCG and TB testing
- reminders (‘immunisations due’) and recall (‘immunisations overdue’) for people who are eligible for vaccination or for parents of infants and children who are

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eligible, as outlined in the Green Book. (This could include written reminders, telephone calls from a member of staff or a computerised auto dialler, text messages or a combination of these approaches.) **[new 2015]**

148. If infants or older children are from disadvantaged families, also offer interventions that provide face-to-face information and advice on the importance of immunisation. These should be delivered by trained lay health workers, community-based healthcare staff or nurses, using community outreach and home visits. [new 2015]

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Improving adherence: case management including directly observed therapy

149. Allocate a named TB case manager to everyone with active TB as soon as possible after diagnosis (and within 5 days). The clinical team should tell each person who their named TB case manager is and provide contact details. [2006, 2012 amended 2015]

150. The TB case managers should work with the person diagnosed with TB to develop a health and social care plan, and support them to complete therapy successfully. The TB case manager should:

- offer an incident risk assessment to every person with TB, to identify their needs and whether they should have enhanced case management including directly observed therapy
- educate the person about TB and the treatment
- develop an individual care plan after discussion with the person
- gain the person's consent to the plan and agree a review date (for example, when moving from initiation to maintenance, or at each contact to ensure the person's needs are being met)
- coordinate discharge planning, especially for people on directly observed therapy
- involve representatives from other allied professions and key workers from all organisations who work with the person if appropriate
- explore appropriate ways that peers and voluntary organisations can provide support. **[2006, 2012, amended 2015]**

151. Offer directly observed therapy as part of enhanced case management in people who:

- do not adhere to treatment (or have not in the past)
- have been treated previously for TB
- have a history of homelessness, drug or alcohol misuse
- are currently in prison, or have been in the past 5 years
- have a major psychiatric, memory or cognitive disorder

- are in denial of the TB diagnosis
- have multidrug-resistant TB
- request directly observed therapy after discussion with the clinical team
- are too ill to administer the treatment themselves. **[2012, amended 2015]**

152. In children whose parents are members of any of the above groups, offer directly observed therapy as part of enhanced case management and include advice and support for parents to assist with treatment completion. [2015]

153. Re-evaluate the need for directly observed therapy throughout the course of TB treatment whenever the person's (or in the case of children, parents') circumstances change. [new 2015]

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154. TB case managers should ensure the health and social care plan (particularly if directly observed therapy is needed) identifies why a person may not attend for diagnostic testing or follow a treatment plan, and how they can be encouraged to do so. It should also include ways to address issues such as fear of stigmatisation, support needs and/or cultural beliefs, and may include information on:

- demographics (for example, age, nationality, place of birth, length of time in UK)
- all current prescribing regimens
- housing needs and living situation, including looked-after children
- substance misuse (drugs or alcohol)
- any contact with the criminal justice system
- the need for hepatitis B and C or HIV testing
- HIV status
- other health conditions (physical or mental)
- communication factors (for example, language and literacy levels)
- ability to access treatment (mobility and transport needs)
- employment or entitlement to benefits
- legal or immigration status (including risk of removal or relocation within the UK)
- any enablers or incentives to overcome anything that is stopping diagnosis or treatment. **[2012, amended 2015]**

155. The health and social care plan should:

- state who will be observing treatment and where (if the person is having directly observed therapy this should be provided at a location that is convenient and accessible to them, for example, at a methadone clinic) **[2012, amended 2015]**

- include actions to take if contact with the person is lost (for example, keeping details of people who might be able to help re-establish contact) **[2012]**
- refer to, and be coordinated with, any other care plan already established for the person **[2012]**
- define the support needed to address any unmet health and social care needs (for example, support to gain housing or other benefits, or to help them access other health or social care services) **[2012, amended 2015]**
- include a commitment from the person to complete their TB treatment **[2012, amended 2015]**
- be supported by frequent contact with any key workers who work with the person. **[2006 amended 2011, amended 2015]**

156. Multidisciplinary TB teams should aim to find people with active TB who are lost to follow-up, or who stop using services before completing diagnostic investigations. They should report all those lost to follow-up to local Public Health England teams, GPs, the referring organisation and specialist outreach teams. [2012]

Other strategies to encourage people to follow their treatment plan

157. To encourage people to follow their treatment plan, involve people in treatment decisions for active or latent TB from the start. Emphasise the importance of following the treatment plan when agreeing the regimen. [2015]

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158. Multidisciplinary TB teams should implement strategies for active and latent TB to encourage people to follow the treatment plan and prevent people stopping treatment early. These could include:

- reminder letters, printed information, telephone calls, texts and apps using an appropriate language **[2006, amended 2015]**
- health education counselling and patient-centred interviews **[2006, amended 2015]**
- tailored health education booklets from quality sources **[2006, amended 2015]**
- home visits **[2006]**
- random urine tests and other monitoring (for example, pill counts) **[2006]**
- access to free TB treatment for everyone (irrespective of eligibility for other NHS care) and information about help with paying for prescriptions **[2006, 2012, amended 2015]**
- social and psychological support (including cultural case management and broader social support) **[new 2015]**
- advice and support for parents and carers **[new 2015]**
- incentives and enablers to help people follow their treatment regimen. **[new 2015]**

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159. TB control boards should ensure services take into account the barriers facing vulnerable migrants who may need treatment, and in particular the stigma they may face. Other issues include the location of services (both geographically and in terms of opening times) and people's language and cultural needs, in terms of the format of advice and the type of information given. [2012, amended 2015]

Strategies in prisons or immigration removal centres

160. On arrival at a prison or immigration removal centre, healthcare professionals should ask all prisoners and detainees (including those being transferred from other establishments) whether they are taking TB medication, to ensure continuity of treatment. [2012]

161. All prisoners and immigration removal centre detainees having treatment for active TB should have a named TB case manager. The case manager should be responsible for contingency planning for discharge from prison or detention. [2012]

162. Prisons and immigration removal centres should ensure multidisciplinary TB staff have access to prisoners and detainees who need treatment (for example, by being given security clearance). [2012]

163. All prisoners having treatment for active TB should have directly observed therapy. [2012]

164. Prison health services should have contingency, liaison and handover arrangements to ensure continuity of care before any prisoner on TB treatment is transferred between prisons or released. In addition, other agencies working with prisoners or detainees should also be involved in this planning. [2012]

165. Prison and immigration removal centre healthcare services should liaise with the named TB case manager (from the multidisciplinary TB team) to ensure contingency plans for continuation of treatment are drawn up for prisoners and immigration removal centre detainees with TB. [2012]

166. Multidisciplinary TB teams should ensure accommodation is available for the duration of TB treatment after the prisoner or detainee's release. [2012]

167. Multidisciplinary TB teams should ensure directly observed therapy is arranged for prisoners or detainees being treated for TB after their release. This should be available close to where they will live in the community. [2012]

168. Multidisciplinary TB teams (in collaboration with Public Health England, primary care, the voluntary sector and Health Education England) should identify and support an ongoing TB education programme for local professionals in contact with the general public, and at-risk groups in particular. This includes, for example, staff in emergency departments, GPs and wider primary care staff, people who work in housing support services, staff who support migrants and those working in walk-in centres, hostels, substance misuse projects and prisons. [2012, amended 2015]

169. Multidisciplinary TB teams should ensure the education programme increases other professionals' awareness of the

possibility of TB and reduces the stigma associated with it. The programme should include detail on:

- causes of TB, how it is transmitted, and the signs and symptoms
- lifestyle factors that may mask symptoms
- local epidemiology, highlighting under-served groups, other high-risk groups and the fact that TB also occurs in people without risk factors
- principles of TB control:
  - early diagnosis and active case-finding
  - how to support treatment (including directly observed therapy)
  - drug resistance
  - awareness of drug interactions (including factors such as effect on contraception efficacy)
  - contact investigation after diagnosing an active case
  - the importance of adhering to treatment
  - treatment for TB is free for everyone (irrespective of eligibility for other NHS care)
  - social and cultural barriers to accessing health services (for example, fear of stigma and staff attitudes)
  - local referral pathways, including details of who to refer and how
  - the role of allied professionals in awareness-raising, identifying cases and helping people complete treatment
  - misinformation that causes fear about TB, including concerns about housing people with the condition
  - the best ways to effectively communicate all the above topics with different groups. **[2012, amended 2015]**

170. Statutory, community and voluntary organisations and advocates working with the general public, and under-served and high-risk groups in particular, should share information on TB education and awareness training with all frontline staff. (They should get information on this from the local multidisciplinary TB team.) [2012, amended 2015]

171. If possible, statutory, community and voluntary organisations should ensure peers from under-served groups and anyone else with experience of TB contribute to, or lead, awareness-raising activities. (Peers who lead such activities will need training and support.) [2012, amended 2015]

172. Multidisciplinary TB teams should help professionals working in relevant statutory, community and voluntary organisations to raise awareness of TB among under-served and other high-risk groups. These professionals should be able to explain that treatment for TB is free and confidential for everyone (irrespective of eligibility

for other NHS care). They should also be able to provide people with details of:

- how to recognise symptoms in adults and children
- how people get TB
- the benefits of diagnosis and treatment (including the fact that TB is treatable and curable)
- location and opening hours of testing services
- referral pathways, including self-referral
- the potential interaction of TB medication with other drugs, for example, oral contraceptives and opioids (especially methadone) and HIV treatment
- TB/HIV co-infection
- how to address the myths about TB infection and treatment (for example, to counter the belief that TB is hereditary)
- how to address the stigma associated with TB
- the risk of migrants from high-incidence countries developing active TB – even if they have already screened negative for it
- contact tracing. **[2012, amended 2015]**

173. Multidisciplinary TB teams and others working with at-risk groups should use high quality material to raise awareness of TB (see section 1.1.2). [2012, amended 2015]

174. Multidisciplinary TB teams and others working with the general public, and with under-served and other high-risk groups in particular, should include information on TB with other health-related messages and existing health promotion programmes tailored to the target group. [2012, amended 2015]

175. Multidisciplinary TB teams should work in partnership with voluntary organisations and 'community champions' to increase awareness of TB, in particular among under-served groups at risk of infection but also in the general population. If possible, peers who have experience of TB should contribute to awareness-raising activities and support people in treatment. [2012, amended 2015]

176. National organisations (for example, National Knowledge Service – Tuberculosis, TB Alert, Public Health England, Department of Health and NHS Choices) should work together to develop generic, quality-assured template materials with consistent up-to-date messages. These materials should be made freely available and designed so that they can be adapted to local needs. [new 2015]

177. Multidisciplinary TB teams should use these templates for general awareness raising and targeted activities in under-served and other high-risk groups. Involve the target group in developing and piloting the materials. [new 2015]

178. The content of any materials should:

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- be up-to-date and attractively designed, including pictures and colour where possible
- be culturally appropriate, taking into account the language, actions, customs, beliefs and values of the group they are aimed at
- be tailored to the target population's needs
- include risks and benefits of treatment, and how to access services, advice and support
- dispel myths
- show that, by deciding to be tested and treated for TB, a person can be empowered to take responsibility for their own health
- use language that encourages the person to believe that they can change their behaviour
- be simple and succinct. **[new 2015]**

179. Make the material available in a range of formats such as written, braille, text messages, electronic, audio (including podcasts), pictorial and video. Make them freely available in a variety of ways, for example, online, as print materials or on memory sticks. [new 2015]

180. Disseminate materials in ways likely to reach target groups, for example, via culturally specific radio or TV stations, at shelters, and at community, commercial or religious venues that target groups attend regularly. [new 2015]

181. Public Health England, in partnership with NHS England, should take responsibility for national oversight of TB prevention and control activities. This includes setting up TB control boards (see Developing the TB prevention and control programme). [2012, amended 2015]

182. Public Health England and NHS England should work together to establish control boards in agreed geographical areas and employ appropriate staff (see recommendation on TB control board staff). [new 2015]

183. Clinical commissioning groups and local authority public health teams working in partnership with Public Health England and NHS England should consider collaborative commissioning arrangements through TB control boards. This could, for example, include working with 1 or more clinical commissioning groups to cover a major metropolitan district, region or TB control board area taking into account:

- local TB incidence
- local at-risk populations and their movements across different geographical areas
- existing service configurations for organisations involved in TB prevention and control
- the need to share services, such as mobile X-ray facilities, across different geographical areas. **[2012, amended 2015]**

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184. TB control boards should develop TB prevention and control programmes working with commissioners, Public Health England and NHS England. The board could include clinical, commissioning (from clinical commissioning groups, local government and the voluntary sector) and public health leaders and people with TB or groups who advocate on their behalf from across the control board area. This may include identifying a lead clinical commissioning group, which could be led by an executive director of that commissioning group working with the board. Develop feedback mechanisms between local commissioning groups and the TB control board. [new 2015]

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185. An executive director of local commissioning groups working with the local director of public health or another nominated public health consultant should lead implementation of the programme in their locality. The lead should ensure a comprehensive prevention and control programme is commissioned to support the level of need (see needs assessment recommendations) and that they work with the control board regularly. [2012, amended 2015]

186. Working together through TB control boards and local networks, commissioners, local government and Public Health England should ensure TB prevention and control programmes set up multidisciplinary TB teams to provide all TB services (see recommendations on commissioning multi-discilinary TB teams). They should ensure that local strategy and service commissioning focuses on an end-to-end pathway. [2012, amended 2015]

187. Working together through TB control boards, commissioners and Public Health England should ensure the TB prevention and control programme is informed by relevant NICE guidance and developed in collaboration with clinical services. It should also be informed by the standard minimum data set collected through local needs assessment and service audit (see needs assessment). [2012, amended 2015]

188. Working together through TB control boards, commissioners and Public Health England should ensure the TB prevention and control programme targets all ages, including children, and covers all aspects of TB prevention and control (see Developing the TB prevention and control programme), including but not limited to:

- active case finding (contact investigations and identifying latent TB in high-risk groups)
- awareness-raising activities
- standard and enhanced case management (including providing directly observed therapy and free treatment)
- finding those lost to follow-up and encouraging them back into treatment
- incident and outbreak control
- monitoring, evaluating and gathering surveillance and outcome data. **[2012, amended 2015]**

189. Working together through TB control boards, commissioners, Public Health England and the voluntary sector should ensure TB prevention and control programmes take account of the need to

work with other programmes targeting specific high-risk groups, such as those who are under-served. Examples include programmes focused on the health of asylum seekers and refugees, under-served children, homelessness and housing, offenders and substance misusers. [2012, amended 2015]

190. Working together through TB control boards, commissioners, Public Health England, the voluntary sector, clinical teams and managers should consider whether TB prevention and control programmes need to develop integrated TB/HIV services. Such services could include joint clinics and training opportunities with medical, nursing and psychosocial input from both TB and HIV specialists. [new 2015]

191. Commissioners should consider offering support and advice to all groups diagnosed with TB irrespective of whether they are under served (see Raising and sustaining awareness of TB). [new 2015]

192. TB control boards should be responsible for developing a TB control programme - based on the national strategy and evidence-based models

[new 2015]

193. TB control boards should plan, oversee, support and monitor local TB control, including clinical and public health services and workforce planning [new 2015]

194. TB control board staff should assess services in their area, identify gaps in provision and develop plans to meet these, including:

- undertaking a workforce review to support local or regional commissioning of TB services to meet the needs of their population
- supporting development of appropriate services and pathways to improve access and early diagnosis
- negotiating arrangements to cover the cost of additional services to address specific gaps in current TB control arrangements. **[new 2015]**

195. TB control boards should ensure cohort review is undertaken at least quarterly (see section 1.8.6), and the results are fed back to local clinical and TB networks. These should be agreed by accountable bodies such as clinical commissioning groups, trust management, regional Public Health England and centre directors and local authority directors of public health as agreed, all of whom should make sure appropriate action is taken. [new 2015]

196. TB control boards should enable full and consistent use of national guidelines including:

197. TB control boards should develop links and partnerships and establish agreed relationships and lines of accountability between TB control boards and local clinical and TB networks. This includes engaging with other key stakeholders to ensure universal coverage of TB control efforts. [new 2015]

198. TB control boards should collaborate with their local and regional partners. They should agree and establish regular monitoring,

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surveillance and reporting arrangements with all partners to support needs assessment (see section 1.8.5) and regular audit and evaluation. [new 2015]

199. TB control board staff should, as a minimum, include a control board director and a manager. Their roles and responsibilities should include:

200. TB control boards should ensure there is enough capacity available to them to manage a sudden increase in demand such as:

201. To set up, monitor and evaluate a TB control programme, TB control boards will need to:

- agree plans within their partnerships to assess local services against the service specifications
- develop plans and quality standards to secure improvements
- establish quality assurance mechanisms and regular audits including but not limited to cohort review for all aspects of the TB control board partnership plans. **[new 2015]**

202. TB control boards should (in collaboration with commissioners) consider the need for a local TB network coordinator, particularly if working across multiple clinical commissioning group areas (see Strategic Oversight recommendation). [new 2015]

203. The coordinator should work in close collaboration with clinicians and all relevant multidisciplinary TB teams to develop the network and be responsible for:

- setting up the network and developing it based on needs, reporting back to the TB control board regularly
- establishing the links, partnerships and relationships across their local network (if necessary across usual geographical commissioning boundaries). **[new 2015]**

204. TB control boards should consider setting up a regional multidisciplinary TB network to discuss multidrug-resistant TB. This could:

- Identify designated regional expert centres.
- Ensure all healthcare professionals who suspect or treat a case of multidrug-resistant TB are informed about, have access to, and are encouraged to use specialist advisory services for multidrug-resistant TB. This includes the designated expert centre in their regional network and may also include the national advisory service for MDRTB (currently provided by the British Thoracic Society).
- Ensure all cases of multidrug-resistant TB are discussed at the regional multidisciplinary TB team meeting in the local clinical network.
- Formally consider and record the advice from the specialist advisory services for multidrug-resistant TB

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provided by the designated regional expert centre or the national advisory service for multidrug-resistant TB. **[new 2015]**

205. Commissioners in rural areas (working with the TB control board) should consider collaborative approaches to deliver and manage TB services. They could, for example, set up a network including areas with high and low incidence of TB to:

- provide general expertise in the condition and offer expert support and advice on more complex cases
- consider pooling administration support and having arrangements for nursing cross-cover during times of illness or annual leave
- share training opportunities for healthcare professionals and consider protected learning time for continuing professional development activities on TB in those who may encounter TB
- agree a shared cohort review process (see cohort review). **[new 2015]**

206. Commissioners should consider using technology to help patients and staff living and working in rural areas overcome issues such as travel. Technology could also be used to manage staff workload, for example allowing them to attend meetings and consultations virtually. [new 2015]

207. Directors of public health, in discussion with local health protection teams, should ensure that TB is part of the joint strategic needs assessment. [2012, amended 2015]

208. Directors of public health should provide commissioners of TB prevention and control programmes and TB control boards (see Strategic oversight recommendations) with local needs assessment information annually using data provided by Public Health England. [2012, amended 2015]

209. Commissioners of TB prevention and control programmes should ensure services reflect the needs of their area, identified by needs assessment. Health and wellbeing boards should ensure that local TB services have been commissioned based on local needs identified through needs assessment. [2012, amended 2015]

210. Directors of public health and TB control boards should use cohort review (see cohort review) and other methods to collect data on the following, to inform local needs assessment:

- Number of annual notified TB cases (see Public Health England's enhanced TB surveillance data and annual 'suite of indicators'). **[2012 amended 2015]**
- Size, composition (for example, age and ethnicity) and distribution of local at-risk groups. **[2012]**
- Indices of social deprivation**.[2012]**
- Local statutory and non-statutory services working with these groups. **[2012]**

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- Organisation of local TB services, including the composition and capacity of the local multidisciplinary TB team (see the results of local audit) and location of services. This may also include data to support evaluating the need for integrated TB/HIV services including joint clinics. **[2012 amended 2015]**
- Numbers needing enhanced case management (see Adherence recommendations and local cohort review reports).**[2012]**
- Numbers receiving directly observed therapy from the start of, or at any point during, treatment (see Public Health England's enhanced TB surveillance data). **[2012]**
- Evidence of recent transmission (for example, using DNA fingerprinting or surrogate markers such as number of cases in children under 5 years (see 'UK TB strain-typing database' and local incident and outbreak reports). **[2012 amended 2015]**
- Completeness and yield of contact investigations. This includes: proportion of sputum-smear-positive cases with 0, 5 or more contacts identified; proportion of identified contacts clinically assessed; and proportion of contacts with latent TB infection who successfully complete treatment (see also contact investigations).
- Active case-finding initiatives, incident contact investigations and identification of latent TB infection in high risk groups **[2012 amended 2015]**
- Treatment outcomes for everyone grouped according to social risk factors and by the use of directly observed therapy (including rates of loss to follow-up and treatment interruptions – see Public Health England's enhanced TB surveillance data and cohort review, case finding and contact investigation reports). **[2012]**
- Local education and awareness-raising programmes for under-served groups, professionals and practitioners working with them. **[2012]**
- Views and experiences of people with TB, carers and the services working with them. **[2012 amended 2015]**

211. Local needs assessments should also be equity proofed to assess the potential effect of planning, commissioning and policy decisions on health inequalities (see planning and commissioning services in NICE's local government briefing on health inequalities and population health). [new 2015]

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212. TB control boards and prevention and control programme leads should initiate, audit and evaluate cohort reviews in their commissioning area. Quarterly cohort review meetings should take place in the area covered by the programme. Combine these meetings with others if possible, or make use of technology to make it easier for clinicians and case managers to attend. [2012, amended 2015]

213. TB case managers should present standardised information on each case, including: demographic information, HIV test results, pre-treatment and ongoing status (clinical, laboratory, radiology), adherence to treatment and the results of contact investigations. [2012, amended 2015]

214. TB case managers and key allied professionals from the TB prevention and control programme should attend cohort review meetings. This could include the lead clinician (who may or may not be the case manager). Either a paediatrician with training and expertise in TB management or a paediatric infectious disease specialist should be present when cases of children with TB are presented. [2012, amended 2015]

215. The chair of the cohort review should not work for any of the TB services included in the review. Examples of possible chairs include a public health consultant, a specialist physician or a senior TB nurse, preferably from a different geographical area. Alternatively the chair could be a representative from the local Public Health England health protection team or the TB control board. [2012, amended 2015]

216. Multidisciplinary TB teams, in conjunction with Public Health England units and the TB control boards, should collate and present cohort review data on TB treatment and the outcome of contact investigations at the review meetings. In addition, progress towards national, regional and local service targets should be presented. [2012, amended 2015]

217. TB control boards directors of public health and local public health consultants should ensure outputs from the cohort review feed into the needs assessment for TB services. TB control board directors should attend the cohort review at least once a year. [2012, amended 2015]

218. TB case managers should feed back promptly to multidisciplinary TB teams on issues identified as a result of cohort review. The results of the cohort review should be collated locally and agreed by the chair before being fed back to TB control boards, commissioners and health and wellbeing boards regularly and via needs assessment. [2012, amended 2015]

219. People participating in a cohort review should review the results and evaluate local services (for example, auditing adverse outcomes, rates of culture confirmation, treatment completion rates or time to diagnosis). [2012, amended 2015]

220. Commissioners should ensure multidisciplinary TB teams:

- Have the skills and resources to manage the care of people with active TB who are not from under-served groups. (A minimum of 1 whole-time equivalent case manager is recommended per 40 incident cases needing standard management.) **[2012, amended 2015]**
- Include at least 1 TB case manager with responsibility for planning and coordinating the care of under-served people and those with active TB who receive enhanced case management. (One whole-time equivalent case

manager is recommended per 20 incident cases needing enhanced case management.) **[2012, amended 2015]**

- Have the resources to manage latent TB care in under-served groups and the wider population. (One whole-time equivalent case manager is recommended per 40 latent TB cases needing enhanced case management and per 80 latent TB cases for standard case management). **[new 2015]** Update 2015
- Include a range of clinical specialties in the multidisciplinary TB team, including paediatrics, infection control and respiratory medicine. **[2012]**
- Have regular attendance at these multidisciplinary team meetings and cohort review meetings for all team members included as a programmed activity as part of their work planning. **[new 2015]** Update 2015
- Have the skills and resources necessary to manage the care of people with complex social and clinical needs (either directly or via an established route). This includes the ability to provide prompt access (or if necessary, referral) to skilled outreach and advocacy workers who can draw on the services of allied practitioners. The aim is to address people's housing, asylum, immigration, welfare, substance dependency and other health and social care needs. (The allied practitioner support should include both a specified housing officer and a social worker.) **[2012]**
- Can provide rapid access TB clinics for all cases, including under-served groups. **[2012]**
- Provide administration support to TB nurses and case managers so they have capacity for clinical and case management work in line with the standard case management or enhanced case management ratios. This should include giving TB nurses access to computer hardware and software. **[new 2015]** Update 2015
- Have the resources to provide a continuous service throughout the year, ensuring the TB service accounts for the following to manage continuity of care:
  - planned absence (for example professional development, mandatory training, annual, maternity or paternity leave)
  - unplanned absence (such as sickness absence). **[2012, amended 2015]**
- Can provide prompt access to a professional who has training and experience in assessing and protecting children and vulnerable adults at risk of abuse or neglect. **[2012]**
- Have access to funds through local government and clinical commissioning groups that can be used flexibly to improve adherence to treatment among under-served groups. For example, funds could be used to provide transport to clinics, to provide support or enablers for

treatment, or for paying outreach workers or community services to support directly observed therapy. Funds may also be used to provide accommodation during treatment (see rapid access TB services recommendations). **[2012, amended 2015]**

- Have the resources to provide ongoing TB awareness-raising activities for professional, community and voluntary (including advocacy) groups that work with populations at high risk of TB (see recommendations on raising and sustaining awareness of TB and Providing information for the public about TB). These resources could be financed by local government or clinical commissioning groups. **[2012, amended 2015]**

221. TB control boards and local TB services should consider employing trained, non-clinically qualified professionals to work alongside clinical teams to agreed protocols, and to contribute to a variety of activities. Examples of this may include awareness raising and supporting patients to attend appointments (including other health and social care appointments). They could also help with collecting samples, contact tracing, case management including directly observed therapy and cohort review, or any other aspect of the service if:
    - they are trained to deliver the intervention or processes effectively
    - they are supported, mentored and supervised by a named case manager such as a TB nurse
    - they have the skills to monitor, evaluate and report on their work practices and outcomes to maintain a process of ongoing evaluation and service improvement in relation to cohort review (see cohort review recommendations). **[new 2015]**
222. TB control boards should ensure that people working in the TB service have the right knowledge, engagement, advocacy and communication skills to meet the needs (for example language, cultural or other requirements) of all the groups they may work with (see needs assessment). [new 2015]
223. Commissioners should consider different needs across traditional geographical and organisational boundaries are taken into account. Put agreements in place so that staff can work across these boundaries, covering the whole service or TB control board area if appropriate. [new 2015]
224. Commissioners and TB control boards should ensure they put in place appropriate governance (including clear lines of accountability and extension of scope of practice) and data sharing practices and agreements. This includes ensuring they are part of service level agreements between NHS and non-NHS services, for example the third sector or local government, and appropriate training has been completed. [new 2015]
225. TB control boards should ensure there is enough capacity available to them to manage a sudden increase in demand such as:

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- TB contact investigations (for example incidents in congregate settings)
- large scale active case finding initiatives in under-served groups in the community
- outbreaks in a variety of settings or sites where transmission risk may be high, including but not limited to schools, workplaces, hostels and prisons. **[new 2015]**

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Active case finding in underseved groups

226. Multidisciplinary TB teams should follow NICE recommendations on contact tracing (see Case finding section).They should coordinate contact investigations at places where the person with TB spends significant amounts of time. Examples could include pubs, crack houses, parks and community centres. The aim is to help identify people who have been living with them and people they frequently socialise. [2012]

227. Multidisciplinary TB teams dealing with someone from an under-served group should work alongside health and social care professionals known to them to help trace relevant contacts. They should also work in partnership with voluntary, community and statutory organisations to conduct outreach contact investigations. [2012]

228. Multidisciplinary TB teams should, if available and appropriate, encourage peer educators or TB programme support workers (see Non-clinical roles including TB support workers) to help with contact investigations involving under-served people who have complex social networks. [2012]

229. Multidisciplinary TB teams in discussion with local Public Health England health protection teams should consider using digital mobile X-ray for active case-finding in settings identified by looking at social networks as places where under-served people at risk congregate. They should also provide the necessary support so that multidisciplinary TB teams can use strain-typing and social network analysis to ascertain where transmission is occurring in the community. (Examples of transmission sites may include pubs, crack houses, hostels and day centres.) They should focus on active case-finding in the settings identified. [2012, amended 2015]

Incident and outbreak response

230. Multidisciplinary TB teams should coordinate incident or outbreak contact investigations at places where the person with TB spends significant amounts of time. Examples include workplaces, schools, colleges, universities, childcare settings. The aim is to help identify people they frequently spend substantial time with as outlined in the Active case finding section. [new 2015]

231. Multidisciplinary TB teams should refer any incident in a congregate setting to the local health protection team for risk assessment within 5 working days of suspicion of a potential incident. They should tell the local TB control board a referral has been made. [new 2015]

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232. TB control boards working with local health protection teams should set up or have access to an incident team that will:

- undertake an incident risk assessment and provide advice
- support or undertake contact investigations
- provide information and communication support to the multidisciplinary TB team, the local director of public health, the setting where the incident has occurred and the people affected including:
  - written advice printed or by email
  - question and answer sessions
  - telephone advice
  - media engagement.
- Gather and collate data, and report on outcomes to measure the effectiveness of the investigation (for example, offering testing to all people identified at risk and monitoring uptake).
- Report back to TB control boards at appropriate times. This includes when outcomes of initial investigation of people classified as close contacts are available. It also includes when a decision is made to broaden the investigation to the next stage using the concentric circle method for risk assessment). **[new 2015]**

233. When incidents have been identified, multidisciplinary TB teams in discussion with local Public Health England health protection teams could also provide support for strain-typing and other analysis to ascertain where transmission is occurring. (Examples of transmission sites may include workplaces, schools, colleges, universities, childcare settings). [new 2015]

234. In all types of contact investigation scenario (active case finding, incident or outbreak investigations) multidisciplinary TB teams should investigate all people who have been in contact with children who have pulmonary or non-pulmonary TB to identify the primary source of infection. If necessary, they should look beyond immediate close contacts to find the source. [2012, amended 2015]

235. Multidisciplinary TB teams should establish relationships with statutory, community and voluntary organisations that work with people at risk of TB to develop appropriate TB referral pathways. They should ensure these organisations know how to refer people to local TB services. [2012]

236. Multidisciplinary TB teams should accept referrals from healthcare providers and allied organisations working in the community with under-served groups. This includes voluntary and statutory organisations (for example, mobile X-ray teams or community organisations or outreach workers working with vulnerable migrants). [2012]

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237. Multidisciplinary TB teams should accept self-referrals to TB clinics by people who suspect they have TB or have recently been in contact with someone with TB. [2012, amended 2015]

238. Multidisciplinary TB teams should consider accepting direct referrals from emergency departments (seerecommendations on Direct referral from emergency departments to multidisciplinary TB teams). [new 2015]

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239. Healthcare professionals should consider urgent referral to TB clinics for people with suspected active TB. They should also ensure the results from first-line diagnostic tests (including a sputum smear and posterior-anterior chest X-ray) are available before the person sees a specialist. (Note: this should not delay the referral.) [2012, amended 2015]

240. Multidisciplinary TB teams should have pathways to triage referrals, start investigations and collect clinical information before the person is seen by a physician. While triaging they should ensure everyone is given information about TB as part of the process (see recommendations on Providing information for the public about TB). This should include who the person should contact if they have any questions and how to access advice or information from support groups, national charities such as TB Alert and other sources such as local government (for example, public health or social care teams). [2015]

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241. Multidisciplinary TB teams should ensure people who have a smear-positive result or imaging features highly suggestive of sputum-smear-positive TB (for example evidence of cavitation on chest X-ray) are assessed the next working day. This is so that case management and infection control procedures start promptly. [2012, amended 2015]

242. The multidisciplinary TB team should assess people who are not sputum-smear-positive but have imaging that suggests pulmonary TB as soon as possible. This should be no later than 5 working days after a referral. [2012, amended 2015]

243. Multidisciplinary TB teams should be able to provide or arrange outreach services to ensure sputum samples or other assessments such as contact investigation can be arranged in the community. [2015]

244. Local hospitals, clinical commissioning groups and the local multidisciplinary team should consider developing a local pathway for patients with imaging highly suggestive of active TB. The pathway should enable them to be referred by the radiology departent by the next working day to multidisciplinary TB teams. Consider including the following in the pathway:

- Agreed standardised radiology codes to identify imaging investigations highly suggestive of active TB.
- Regular liaison between multidisciplinary TB teams and the radiology department (for example weekly) to ensure all patients have been referred to the multidisciplinary team for triage using the agreed local mechanism or pathway. **[new 2015]**

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245. Report results of all pathology or other diagnostic results suggesting TB to the multidisciplinary TB team and clinician requesting them. [new 2015]

246. Commissioners and multidisciplinary teams should consider working with emergency departments to develop direct referral pathways for people with suspected TB so that:

- the local multidisciplinary team is informed of all suspected cases of TB using the appropriate process
- referral is accepted from any appropriate healthcare professional, for example an on-call radiologist. **[new 2015]**

247. Emergency department clinicians should ensure first-line diagnostic tests for TB are performed (see table 1 in recommendation 33). [new 2015]

248. Emergency departments should consider carrying out audits of their direct referrals because of suspected TB and the outcomes of diagnosis. [new 2015]

249. Multidisciplinary TB teams should consider training emergency department staff in:

- using approaches that do not stigmatise people with TB
- giving people with TB appropriate advice. **[new 2015]**

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250. Multidisciplinary TB teams, prisons, custody suites and immigration removal centre healthcare services should have named TB liaison leads to ensure they can communicate effectively with each other. [2012, amended 2015]

251. Prison, custody suites and immigration removal centre healthcare services should develop a TB policy by working with the TB control board and multidisciplinary TB team and the local Public Health England health protection team. [2012, amended 2015]

252. Multidisciplinary TB teams, in conjunction with prisons, custody suites and immigration removal centre healthcare services, should agree a care pathway for TB. This is to ensure that any suspected or confirmed cases are reported to, and managed by, the multidisciplinary TB team. [2012, amended 2015]

253. Multidisciplinary TB teams, in liaison with prisons, custody suites or immigration removal centre healthcare providers, should manage all cases of active TB. Investigations and follow-up should be undertaken within the prison or immigration removal centre if possible. [2012, amended 2015]

254. Multidisciplinary TB teams should assess the living circumstances of people with TB. Where there is a housing need they should work with allied agencies to ensure that all those who are entitled to state-funded accommodation receive it as early as possible during their treatment. [2012]

255. Multidisciplinary TB teams, commissioners, local authority housing lead officers and other social landlords, providers of hostel accommodation, hospital discharge teams, Public Health England and the Local Government Association should work together to agree a process for identifying and providing

accommodation for homeless people diagnosed with active pulmonary TB who are otherwise ineligible for state-funded accommodation. This includes people who are not sleeping rough but do not have access to housing or recourse to public funds. The process should detail the person's eligibility and ensure they are given accommodation for the duration of their TB treatment. [2012, amended 2015]

256. Local Government and clinical commissioning groups should fund accommodation for homeless people diagnosed with active TB who are otherwise ineligible for state-funded accommodation. Use health and public health resources, in line with the Care Act 2014. [2012, amended 2015]

257. Multidisciplinary TB teams should make people who would not otherwise be entitled to state-funded accommodation aware that they may lose this accommodation if they do not comply with treatment. They should ensure plans are made to continue housing people once their TB treatment is completed. [2012]

258. Public Health England, working with the Local Government Association and their special interest groups, should consider working with national housing organisations such as the Chartered Institute of Housing and the National Housing Federation to raise the profile of TB. This is to ensure people with TB are considered a priority for housing. Consider developing and delivering training on TB and the need for housing support for their members. [new 2015]

Update 2015

259. Once a person has been diagnosed with active TB, the diagnosing physician should inform relevant colleagues so that the need for contact tracing can be assessed without delay. Contact tracing should not be delayed until notification. [2006]

260. Offer screening to the household contacts of any person with pulmonary TB. Household contacts are defined as those who share a bedroom, kitchen, bathroom or sitting room with the index case. [2006, amended 2015]

261. Assess symptomatic household contacts for active TB. [new 2015]

Update 2015

262. In asymptomatic household contacts younger than 65 years, consider standard testing for latent TB, followed by consideration of BCG (see section 1.1.3) or treatment for latent TB infection (see section 1.2.2) once active TB has been ruled out (see section 1.3.1) for people who:

- are previously unvaccinated, and
- are household contacts of a person with sputum-smear-positive TB, and
- are Mantoux negative (see section 1.2.1). **[2006, amended 2015]**

263. In asymptomatic household contacts older than 65 years, consider a posterior-anterior chest X-ray (if there are no contraindications), possibly leading to further investigation for active TB. [2006, amended 2015]

264. For people with pulmonary TB, assess other close contacts. These may include boyfriends or girlfriends and frequent visitors to the home of the index case. Occasionally, a workplace associate may be judged to have had contact equivalent to that of household contacts, and should be assessed in the same way. [2006, amended 2015]

265. Do not routinely assess casual contacts of people with TB, who will include most workplace contacts. [2006, amended 2015]

266. Assess the need for tracing casual contacts of people with pulmonary TB if:

- the index case is judged to be particularly infectious (for example, evidenced by transmission to close contacts), or
- any casual contacts are known to possess features that put them at high risk of going on to develop active TB. **[2006, amended 2015]**

267. Offer 'inform and advise' information to all contacts of people with smear-positive TB. [2006]

268. After diagnosis of TB in an aircraft traveller, do not routinely carry out contact tracing of fellow passengers. [2006, amended 2015]

269. The notifying clinician should inform the relevant consultant in communicable disease control or health protection if:

- less than 3 months has elapsed since the flight and the flight was longer than 8 hours, and
- the index case is sputum-smear-positive, and either
- the index case has multidrug-resistant TB, or
- the index case coughed frequently during the flight. **[2006]**

270. The consultant in communicable disease control or health protection should provide the airline with 'inform and advise' information to send to passengers seated in the same part of the aircraft as the index case. [2006]

271. If the TB index case is an aircraft crew member, contact tracing of passengers should not routinely take place. [2006]

272. If the TB index case is an aircraft crew member, contact tracing of other members of staff is appropriate, in accordance with the usual principles for screening workplace colleagues. [2006]

273. After diagnosis of TB in a school pupil or member of staff, the consultant in communicable disease control or health protection should be prepared to explain the prevention and control procedures to staff, parents and the press. Advice on managing these incidents and their public relations is available from the Public Health England Health Protection Team and the local authority. [2006, amended 2015]

274. If a school pupil is diagnosed with sputum-smear-positive TB, carry out a risk assessment of the need to test the rest of his or her class (if there is a single class group), or the rest of the year group who share classes, as part of contact tracing. [2006]

275. If a teacher has sputum-smear-positive TB, assess the pupils in his or her classes during the preceding 3 months as part of contact tracing. [2006]

276. Consider extending contact tracing in schools to include children and teachers involved in extracurricular activities, and non-teaching staff, on the basis of:

- the degree of infectivity of the index case
- the length of time the index case was in contact with others
- whether contacts are unusually susceptible to infection
- the proximity of contact. **[2006, amended 2015]**

277. Treat secondary cases of sputum-smear-positive TB as index cases for contact tracing. [2006]

278. If the index case of a school pupil's TB infection is not found, and the child is not in a high-risk group for TB, contact tracing and screening (by either symptom enquiry or chest X-ray) should be considered for all relevant members of staff at the school [2006]

279. When an adult who works in childcare (including people who provide childcare informally) is diagnosed with sputum-smear-positive TB, manage as for contact tracing. [2006]

280. If TB is diagnosed in a hospital inpatient, do a risk assessment. This should take into account:

- the degree of infectivity of the index case
- the length of time before the infectious patient was isolated
- whether other patients are unusually susceptible to infection
- the proximity of contact. **[2006, amended 2015]**

281. Carry out contact tracing and testing only for patients for whom the risk is regarded as significant. [2006]

282. Regard patients as at risk of infection if they spent more than 8 hours in the same bay as an inpatient with sputum-smear-positive TB who had a cough. Document the risk in the contact's clinical notes, for the attention of the contact's consultant. Give the contact 'inform and advise' information, and inform their GP. [2006]

283. If patients were exposed to a patient with sputum-smear-positive TB for long enough to be equivalent to household contacts (as determined by the risk assessment), or an exposed patient is known to be particularly susceptible to infection, manage their TB risk in the same way as household contacts. [2006, amended 2015]

284. If an inpatient with sputum-smear-positive TB is found to have multidrug-resistant TB, or if exposed patients are HIV positive, trace contacts following the Interdepartmental Working Group on Tuberculosis guidelines. [2006]

285. In cases of doubt when planning contact tracing after diagnosing sputum-smear-positive TB in an inpatient, seek further advice from the local or national Public Health England or Wales unit or people experienced in the field. [2006, amended 2015]

286. In areas of identified need (see section 1.8.6), including major urban centres with a high incidence of TB, commissioners should:

- ensure there is a programme of active case-finding using mobile X-ray in places where homeless people and people who misuse substances congregate (this includes: homeless day centres, rolling shelters, hostels and temporary shelters established as part of cold weather initiatives and venues housing needle and syringe programmes)
- base the frequency of screening at any one location on population turnover
- where local demand does not warrant a mobile X-ray team, consider commissioning mobile X-ray capacity from another area. **[2006, amended 2012]**

287. Multidisciplinary TB teams should consider using simple incentives, such as providing hot drinks and snacks, to encourage people to attend for screening. [2006, amended 2012, amended 2015]

288. Commissioners of TB prevention and control programmes should consider offering people who are homeless and people who misuse substances other health interventions when they are screened for TB at a mobile X-ray unit. (Examples may include blood-borne virus screening, dentistry and podiatry services.) [2012]

289. Multidisciplinary TB teams should work closely with mobile X-ray teams and frontline staff in hostels and day centres to promote TB screening and to ensure appropriate onward referrals and follow-up. [2012]

290. Multidisciplinary TB teams should consider using peer educators to promote the uptake of TB screening in hostels and day centres. [2012]

291. Multidisciplinary TB teams should provide routine data to TB control boards on: screening uptake, referrals and the number of active TB cases identified. [2012]

292. Employees new to the NHS who will be working with patients or clinical specimens should not start work until they have completed a TB screen or health check, or documentary evidence is provided of such screening having taken place within the preceding 12 months. [2006]

293. Employees new to the NHS who will not have contact with patients or clinical specimens should not start work if they have signs or symptoms of TB. [2006]

294. Health checks for employees new to the NHS who will have contact with patients or clinical materials should include:

- assessment of personal or family history of TB

- asking about symptoms and signs, possibly by questionnaire
- documentary evidence of TB skin (or interferon-gamma release assay) testing and/or BCG scar check by an occupational health professional, not relying on the applicant's personal assessment
- Mantoux result within the past 5 years, if available. **[2006]**

295. See recommendations 19 to 22 for screening new NHS employees for latent TB. [2006]

296. Employees who will be working with patients or clinical specimens and who are Mantoux negative should have an individual risk assessment for HIV infection before BCG vaccination is given. [2006, amended 2015]

297. Employees of any age who are new to the NHS and are from countries of high TB incidence, or who have had contact with patients in settings with a high TB prevalence should have an interferon-gamma release assay. If negative, offer BCG vaccination as with a negative Mantoux result. If positive, refer the person for clinical assessment for diagnosis and possible treatment of latent infection or active disease. [2006, amended 2011]

298. If a new employee from the UK or other low-incidence setting, who has not had a BCG vaccination, has a positive Mantoux test (see section 1.2.1) and a positive interferon-gamma release assay, they should have a medical assessment and a posterior-anterior chest X-ray. They should be referred to a TB clinic to determine whether they need TB treatment if the chest X-ray is abnormal, or to determine whether they need treatment of latent TB infection if the chest X-ray is normal. [2006, amended 2011, amended 2015]

299. If a prospective or current healthcare worker who is Mantoux negative declines BCG vaccination, explain the risks and supplement the oral explanation with written advice. If the person still declines BCG vaccination, he or she should not work where there is a risk of exposure to TB. The employer will need to consider each case individually, taking account of employment and health and safety obligations. [2006]

300. Screen clinical students, agency and locum staff and contract ancillary workers who have contact with patients or clinical materials for TB to the same standard as new employees in healthcare environments, according to the recommendations set out above. Seek documentary evidence of screening to this standard from locum agencies and contractors who carry out their own screening. [2006]

301. NHS trusts arranging care for NHS patients in non-NHS settings should ensure that healthcare workers who have contact with patients or clinical materials in these settings have been screened for TB to the same standard as new employees in NHS settings. [2006]

302. Include reminders of the symptoms of TB, and the need for prompt reporting of such symptoms, with annual reminders about occupational health for staff who:

- are in regular contact with TB patients or clinical materials, or
- have worked in a high-risk clinical setting for 4 weeks or longer.

Give one-off reminders after a TB incident on a ward. **[2006]**

303. If no documentary evidence of previous screening is available, screen staff in contact with patients or clinical material who are transferring jobs within the NHS as for new employees. [2006]

304. Assess the risk of TB for a new healthcare worker who knows he or she is HIV positive at the time of recruitment as part of the occupational health checks. [2006]

305. The employer, through the occupational health department, should be aware of the settings with increased risk of exposure to TB, and that these pose increased risks to HIV-positive healthcare workers. [2006]

306. Healthcare workers who are found to be HIV positive during employment should have medical and occupational assessments of TB risk, and may need to modify their work to reduce exposure. [2006]

307. Healthcare professionals in prisons and immigration removal centres should ensure prisoners and detainees are screened for TB within 48 hours of arrival. [2012]

308. Prisons with Department of Health-funded static digital X-ray facilities for TB screening should X-ray all new prisoners and detainees (including those being transferred from other establishments) if they have not had a chest X-ray in the past 6 months. This should take place within 48 hours of arrival. [2012]

309. Prison and immigration removal centre health staff should report all suspected and confirmed TB cases to the local multidisciplinary TB team within 1 working day. [2012]

310. Multidisciplinary TB staff should visit every confirmed TB case in a prison or immigration removal centre in their locality within 5 working days. [2012]

311. If a case of active TB is identified, the local Public Health England unit, in conjunction with the multidisciplinary TB team, should plan a contact investigations exercise. They should also consider using mobile X-ray to check for further cases. [2012]

1.6 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1. Which strategies and interventions are effective and cost effective in promoting the uptake of diagnostic efforts for people with suspected latent TB, and in promoting the uptake of and adherence to treatment in those with a positive diagnosis?

Why this is important

Identifying and effectively treating people with latent TB is a cornerstone of TB control. Encouraging people at risk of infection to be tested and have treatment is therefore vital. Despite this, the Committee found little evidence on strategies to promote these. Randomised controlled trials in at-risk populations are needed.

2. In people with suspected TB, what is the relative clinical and cost effectiveness of a universal approach compared to a risk-based approach to using rapid nucleic acid amplification tests?

Why this is important

The GDG noted that there were 2 possible approaches to using rapid nucleic acid amplification tests for suspected TB. The current approach is to use them only if TB is strongly suspected and rapid information about mycobacterial species would alter the person's care. Another approach is to use them in anyone with a possible diagnosis of TB. There is a trade-off between ensuring that all people with active TB are diagnosed and avoiding a large number of false positives, which lead to unnecessary treatment. This trade-off may lead to differences in the cost effectiveness of each approach. NICE's systematic review of the diagnosis of active TB did not identify any robust evidence on this, nor did the health technology assessment on using nucleic acid amplification tests to detect drug resistance. Cost-effectiveness studies are needed to improve understanding in this area.

3. Is it more cost effective to organise rapid diagnostic services in local or centralised laboratories?

Why this is important

The relative clinical and cost effectiveness of rapid diagnostic tests may be heavily influenced by whether the services delivering them are arranged locally or in centralised laboratories. The organisation of laboratory services may affect the time taken to start appropriate treatment, with subsequent effects on morbidity and mortality rates. In terms of cost effectiveness, there is a balance between these factors and the relative costs of providing localised and centralised services. UK-based cost-effectiveness studies are needed to improve service organisation.

4. How accurate, effective and cost effective are point-of-care diagnostics?

Why this is important

Update 2015

Point-of-care diagnostics may shorten the time between suspicion of disease or drug resistance and starting appropriate treatment. However, NICE identified no evidence in this area. The diagnostic accuracy of these tests should be compared with those currently used, in cross-sectional and cost-effectiveness studies, to determine whether they have a place in UK practice. Outcomes should also include time waiting for results and the cost effectiveness of the tests.

5. Apart from culture, what other diagnostic tests or combinations of tests are effective in establishing an accurate diagnosis of active respiratory TB in children and young people with suspected active TB?

Why this is important

The Committee noted the paucity of evidence on the diagnosis of active TB in children. The disease manifests differently in children than in adults, and more evidence would have been useful to the Committee. Cross-sectional studies are needed to examine the relative accuracy of different tests, and the most appropriate specimen type for these tests, compared with those currently in use. In particular, the poor accuracy of many tests in children means that diagnostic strategies – that is, combinations of tests – should be investigated, including both tests with high sensitivity and those based on host response.

6. In people with suspected TB disease, which fluid or tissue samples provide the highest accuracy in nucleic acid amplification tests?

Why this is important

In order to maximise the accuracy of nucleic acid amplification tests in the diagnosis of active TB disease, the GDG felt that additional information regarding the type of optimal specimen – tissue compared to fluid – would have been useful to their decision-making. The reviews conducted found only limited evidence for this. Cross-sectional studies of nucleic acid amplification tests using linked specimens – that is, tissue and fluid specimens taken from and compared in the same person – should be conducted.

7. How should the standard recommended regimen for active TB be adapted to accommodate comorbidities or coexisting conditions?

Why this is important

NICE conducted an evidence review into the most effective regimens for active TB in people with comorbidities or coexisting conditions (including HIV, liver disease, renal disease, diabetes, substance use, including methadone use, pregnancy and breastfeeding and impaired vision or eye disease), but did not identify any evidence. People in these groups are at increased risk of drug–drug, and do not respond to anti-TB therapy in the same was as those without a comorbidity or coexisting condition. They may therefore need an adapted regimen to improve the likelihood of treatment success and reduce the risk of adverse events. Randomised controlled trials are needed to compare the standard recommended regimen with alternatives for active TB in these people. Alternatively, given the relatively small numbers of people in these groups,

prospective observational cohort studies could be conducted to assess treatment success and adverse events for different regiments.

8. For people with active, drug susceptible TB who experience treatment interruptions because of adverse events, particularly hepatotoxicity, what approach to re-establishing treatment is most effective in reducing mortality and morbidity?

Why this is important

There is little evidence on re-establishing treatment after interruptions because of adverse events. This is key to ensuring treatment success without relapse or the emergence of drug resistance, but avoiding of further adverse events is also important. Randomised controlled trials are needed to compare approaches to re-establishing treatment for active, drug susceptible TB after it is interrupted because of adverse events, particularly hepatotoxicity. These trials should assess mortality, treatment success or failure, rates of relapse, the recurrence of adverse events and the emergence of drug resistance. Approaches evaluated could compare, for example, restarting regimens with lengthening their duration, as well as sequential reintroduction. Approaches should vary depending on the proportion of doses missed and the stage of treatment (initial or continuation phase) in which the interruption occurred. Prospective observational cohort studies with multivariable analyses may also be useful.

9. What are the costs of adverse events, particularly hepatotoxicity, in people who are undergoing treatment for TB, including effects on quality of life?

Why this is important

The health economists for this guidance were unable to identify reliable data on how adverse events affected quality of life and costs in people being treated for TB. Such data are essential in producing economic models that reflect the real costs of treatment. Data need to be collected and reported on the quality of life and other costs of adverse events, particularly hepatotoxicity, experienced by people being treated for TB.

10. Combine data from different national and local registries to improve data use.

Why this is important

There are gaps in the evidence base for several areas of the guideline. These include the best approach to re-establishing treatment after an interruption and the optimal duration of isolation for infection control. The Committee acknowledged that there are excellent sources of information available - such as cohort review databases, the London TB database and the national Enhanced TB Surveillance System database - but these are not linked in any way. A study group with access to these registries and databases could focus on identifying people who have:

- experienced treatment interruptions, and link the management approach to outcomes such as mortality, treatment failure, relapse and drug resistance, as well as to costs; or

- undergone isolation, and link the duration of isolation to TB infection rates, treatment outcomes, measures of quality of life and costs.

11. For isoniazid-resistant TB, what is the most effective regimen for reducing mortality and morbidity?

Why this is important

There is little evidence for the treatment of isoniazid resistant TB. This is the most common form of drug resistance in the UK, occurring in 7.5% of TB cases. Currently, treatment isn't always successful, even when the recommended drugs are given for the recommended time and there are no adherence issues. It is particularly difficult to treat if there are treatment interruptions or if the central nervous system is involved. Randomised controlled trials are needed to compare different anti-TB regimens for isoniazid-resistant TB, assessing mortality, treatment success or treatment failure, rates of relapse and adverse events.

12. What effects does isolation have on the quality of life of people being treated for TB?

Why this is important

Isolation is known to significantly affect a person's quality of life. Despite this, the Committee identified no reliable data on the impact of isolation on quality of life . This information is essential in producing economic models that reflect the real costs of isolation. Data on the impact of isolation on quality of life need to be collected and reported.

13. For people with latent TB, are shorter regimens effective in preventing the development of active TB? If so, which regimen is the most effective?

Why this is important

Shorter regimens with minimal side-effect profiles would help encourage people with latent TB to have and adhere to treatment. Randomised controlled trials comparing the effectiveness of shorter regimens, such as those containing rifabutin or rifapentine, with the current standard regimen (6 month of isoniazid and 3 month of isoniazid and rifampicin) in preventing the development of active TB are needed. Measurements are also needed of the incidence of adverse events, particularly hepatotoxicity. The systematic reviews for this guideline noted the increased risk of hepatotoxicity associated with pyrazinamide-containing regimens. Given this, the Committee , did not feel that these regimens need be investigated further. Trials would need to be of sufficient size to take into account the low rate of progression from latent to active TB.

14. Strategies to improve treatment completion in those infected with latent TB infection and at risk of non-adherence

Is Directly Observed preventative Therapy (DOPT) and other support strategies effective and cost effective compared self-administered therapy in promoting the uptake of and adherence to treatment in those populations who should be offered DOT as part of enhanced case management for active TB?

Why this is important

Effectively treating people with latent TB is considered a cornerstone of TB control. Supporting people at risk of non-adherence to treatment is therefore vital to these efforts. Despite this, little evidence was identified on the effectiveness or cost effectiveness of DOPT in groups at high risk of non-adherence. Randomised controlled trials in these populations should be conducted.

15. Support strategies to improve treatment completion in those infected with active TB

Are peer support workers, non-clinical support workers effective and cost effective compared self-administered therapy and traditional clinical staff (i.e. TB nurses) in reducing time to diagnosis, promoting diagnostic testing uptake, adherence to treatment and improving contact tracing in under-served and high risk groups. What barriers and facilitators can impact on the effectiveness and cost effectiveness of these interventions?

Why this is important

The GDG noted that there was evidence that various support strategies using trained peers or non-clinical staff were effective in supporting TB control efforts although there was non-available from the UK. They also noted there was no consistent evidence comparing these outcomes to normal care (i.e. TB control nurses) or self-administered therapy, or in assessing the cost effectiveness of these interventions to normal care. Further, there was no systematic information on the barriers and facilitators that may affect these outcomes when comparing clinical and non-clinical staff in delivering the same interventions. The GDG considered these interventions to be of particular importance to under-served and high risk groups. Randomised controlled trials and qualitative assessment of the impact in these populations should be conducted.

16. Organisation of TB prevention and control services through TB control boards

Are TB control boards effective and cost effective?

Why this is important

Throughout their discussions, the GDG were aware of the new developments and funding for supporting TB prevention and control efforts in the UK namely the National Strategy and the ring fenced monies being made available to support the national strategy through development of TB Controls

Boards across the UK. The organisation of TB prevention and control activities through more regionalised mechanisms such as TB control boards was considered to be a corner stone of improving TB service delivery and reducing variation, improving access to expertise with the potential to impact the time taken to diagnose TB and initiate appropriate treatment, support treatment completion and improve contact tracing all of which should have downstream impacts on overall morbidity and mortality rates. Quantitative, qualitative and process evaluations of TB control boards using a mixed methods approach to include benchmarking against relevant NICE guideline recommendations and on-going evaluation of surveillance data are recommended.

17. Referral mechanisms and their impact on reducing time to diagnosis

Are rapid radiological referral and direct referral from emergency departments effective and cost effective at reducing time to diagnosis and diagnostic uptake compared to current practice.

Why this is important

The GDG consider time to diagnosis a key outcome in managing TB prevention and control both in terms of outcomes for the person affected but also in reducing transmission risk to the general population. There was some strong evidence available on the effectiveness of a rapid referral process in one area of the UK but as the population served has a particular epidemiology this created some uncertainty when extrapolating this evidence to the population as a whole, other than audit data there there was no empirical evidence for emergency department referral but given the part of the health services contact with certain high risk groups who may not have a GP this mechanism needs further evaluation. Furthermore, neither process had cost-effectiveness evaluations available.

2 Methodology

2.1 CG33 [2006]

2.1.1 Aim

With this document the National Collaborating Centre for Chronic Conditions (NCC-CC) has aimed to provide a user-friendly, clinical, evidence-based guideline for the NHS in England and Wales that:

- offers best practice advice for TB
- is based on best published evidence and expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of the care provision for tuberculosis such as the diagnosis and management of both latent and active TB, and measures for its prevention and control
- indicates areas suitable for clinical audit
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences (full version, short version, quick reference guide and public version) in electronic or printed format.

In contrast to most clinical guidelines commissioned by NICE, the prevention and control sections of this guideline include recommendations on service organisation where good quality evidence exists to support them.

2.1.2 Scope

The guideline was developed in accordance with a specified scope, which detailed the remit of the guideline originating from the Department of Health (DH) and specified those aspects of TB to be included and excluded.

Before development of the guideline began, the scope was subjected to stakeholder consultation in accordance with processes established by NICE.{1}(National Institute for Health and Clinical Excellence 2005) The scope is given in Appendix B.

2.1.3 Audience

The guideline is intended for use with the following people or organisations:

- all healthcare professionals
- people with, or at risk from, tuberculosis, and their carers
- patient support groups
- commissioning organisations
- service providers.

Involvement of people with TB

The NCC-CC was keen to ensure the views and preferences of people with TB and their carers informed all stages of the guideline. This was achieved by:

- consulting the Patient Information Unit (PIU) housed within NICE during the pre-development (scoping) and final validation stages of the guideline

- having two former TB patients and two user organisation representatives on the Guideline Development Group (GDG).

The patient and carer representatives were present at every meeting of the GDG. They were therefore involved at all stages of the guideline development process and were able to consult with their wider constituencies.

2.1.4 Guideline limitations

These include:

- the diagnosis and treatment chapters of this guideline (5–10), except rapid diagnostic techniques (5.3 and 5.4), do not cover issues of service delivery, organisation or provision (as this was not specified in the remit from the DH)
- NICE is primarily concerned with health services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors
- Generally the guideline does not cover rare, complex, complicated or unusual conditions.

2.1.5 Other work relevant to the guideline

Readers of this guideline should also be aware of the following publications:

- *Stopping tuberculosis in England and Wales*, the Chief Medical Officer's TB Action Plan{2}
- *Immunisation against infectious disease* (the 'Green Book'){3}
- *The clinical and cost-effectiveness of diagnostic tests for the detection of mycobacterial infection*, a health technology appraisal due for publication mid 2006 (see www.ncchta.org).

The National Knowledge Service is a relatively new national NHS body which is investigating ways of making patient and public information available to patients and the NHS, amongst other functions. One of the initial pilot projects is in tuberculosis, and is linked to this guideline. See www.hpa.org.uk/tbknowledge for more detail.

The Secretary of State for Health is advised on broader national policy on vaccination by the DH's Joint Committee on Vaccination and Immunisation (JCVI) (http://www.dh.gov.uk/ab/jcvi/index.htm).

Information on TB epidemiology in the UK and abroad, as well as some background information for patients and the public, is available through the Health Protection Agency's website at www.hpa.org.uk. This is referred to at relevant points in this guideline.

2.1.6 Related NICE guidance

Published

- Medicines adherence NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/cg76

2.1.7 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual{1}

(www.nice.org.uk/page.aspx?o=201982) and the methodology pack{4} specifically developed by the NCC-CC for each chronic condition guideline (http://www.ncgc.ac.uk/). The developers' roles and remit are summarised below.

National Collaborating Centre for Chronic Conditions[5]

The National Collaborating Centre for Chronic Conditions (NCC-CC) was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the NICE.

A multiprofessional partners board inclusive of patient groups and NHS management governs the NCC-CC.

NCC-CC technical team

The technical team met approximately two weeks before each GDG meeting and comprised:

- the GDG group leader
- the GDG clinical advisor
- an information scientist
- a research fellow
- a health economist
- a project manager
- administrative personnel.

Guideline Development Group

The GDG met monthly for 15 months (2004 to 2005) and comprised a multidisciplinary team of professionals, service users, carers and user organisation representatives who were supported by the technical team.

The GDG membership details including patient representation and professional groups are detailed in the GDG membership section in appendix K

(Members of the GDG declared any interests in accordance with the NICE technical manual. A register is available from the NCC-CC for inspection upon request (ncc-cc@rcplondon.ac.uk).) (enquiries@ncgc.ac.uk/).

Guideline Project Executive

The Project Executive was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.

The Project Executive comprised:

- the NCC-CC director
- the NCC-CC manager
- an NCC-CC senior research fellow
- the NICE commissioning manager
- the technical team.

5 In April 2009 the NCC-CC merged with three other national collaborating centres, to form the National Clinical Guideline Centre (NCGC)

Sign-off workshop

At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

2.1.8 The process of guideline development

There are nine basic steps in the process of developing a guideline.

First step: Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions. See Appendix A for details of the questions.

Second step: Systematically searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. Conference paper abstracts and non-English language papers were excluded from the searches. The research fellow identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See Appendix A for literature search details.

Third step: Critically appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general no formal contact was made with authors however there were *ad hoc* occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the Technical Manual{1}
- NCC-CC Quality Assurance document & Systematic Review paper available at (http://www.ncgc.ac.uk)

Fourth step: Distilling and synthesising the evidence and writing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

Evidence tables are available at www.rcplondon.ac.uk/pubs/books/TB/index.asp

Fifth step: Grading the evidence statements and recommendations

The evidence statements and recommendations were graded in accordance with Table 2. The level of evidence and classification of recommendations were also included for diagnostic studies.

Table 2: Hierarchy of evidence and recommendation classification

Levels of evidence		**Classification of recommendations**	
Level	Type of evidence	Class	Evidence
1++	High-quality meta-analysis (MA), systematic reviews (SR) of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.	A	Level 1++ and directly applicable to the target population *or* level 1+ and directly applicable to the target population **AND** consistency of results. Evidence from NICE technology appraisal.
1+	Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias.		
1−	MA, SR of RCTs, or RCTs with a high risk of bias.	Not used as a basis for making a recommendation.	
2++	High-quality SR of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.	B	Level 2++, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 1++ or 1+.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.		
2−	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Not used as a basis for making a recommendation.	
3	Non-analytic studies (for example case reports, case series).	C	Level 2+, directly applicable to the target population and demonstrating overall consistency of results *or* extrapolated evidence from 2++.
4	Expert opinion, formal consensus.	D	Level 3 or 4 *or* extrapolated from 2+ *or* formal consensus *or* extrapolated from level 2 clinical evidence supplemented with health economic modelling.
		D (GPP)	A good practice point (GPP) is a recommendation based on the experience of the GDG.
Diagnostic study level of evidence and classification of recommendation was also included.			

Sixth step: Health economic evidence

Due to the appointment of the health economist midway through the guideline development, the areas for health economic modelling were considered after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained

to and agreed by the GDG members during meetings, and they also commented on subsequent revisions.

Seventh step: Agreeing the recommendations

The sign-off workshop employed formal consensus techniques{1} to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The sign-off workshop also reached agreement on the following:

- seven key priorities for implementation
- eight key research recommendations
- five algorithms.

In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly.

The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation.

Eighth step: Structure of the full version of the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and is described below:

The clinical introduction sets a succinct background and describes the current clinical context.

The methodological introduction describes any issues or limitations that were apparent when reading the evidence base.

Evidence statements provide a synthesis of the evidence base and usually describe what the evidence showed in relation to the outcomes of interest.

Health economics presents an overview of the cost-effectiveness evidence base of relevance to the area under address.

'From evidence to recommendations' highlights the debate of the GDG. This section sets out the GDG decision-making rationale, providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.

The recommendations section provides stand-alone, action-orientated recommendations.

Evidence tables are not published as part of the full guideline but are available online at www.rcplondon.ac.uk/pubs/books/TB/index.asp. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

Ninth step: Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed at the NICE website (www.nice.org.uk). Editorial responsibility for the full guideline rests with the GDG7.

Table 3 describes the various versions of the guideline that are available.

Table 3: Versions of this guideline

Versions	Comments
Full version	Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at www.rcplondon.ac.uk/pubs/books/TB/index.asp
NICE version	Documents the recommendations without any supporting evidence. Available at www.nice.org.uk/page.aspx?o=guidelines.completed
Quick reference guide	An abridged version. Available at www.nice.org.uk/page.aspx?o=guidelines.completed
Information for the public	A lay version of the guideline recommendations. Available at www.nice.org.uk/page.aspx?o=guidelines.completed

2.1.99 Healthcare needs assessment

In contrast to many NICE guidelines, the scope requires service guidance in the prevention and control chapters of this guideline (chapters 11–13) and for rapid diagnostic techniques (sections 5.3 and 5.4). The NCC-CC conducted a rapid and simple healthcare needs assessment in order to establish current practice and resources, and to identify areas where these did not match the clinical need. This collected information through a review of the epidemiology of TB in England and Wales, and a review of current service by questionnaire among a sample of TB service providers.

Review of epidemiology

At the outset of the guideline development the prevention and control research fellow, Dr Ian Lockhart, compiled epidemiological data relevant to England and Wales from a number of national sources into a report to inform GDG discussions. This was refined through discussion at GDG meetings, is presented in this guideline in the Appendix K and in section 4.2, and will be described in a forthcoming paper.

Survey of current services

The NCC-CC sought information on current service provision in terms of staffing, location of specific services and caseload. Dr Sooria Balasegaram coordinated this survey through TB nurses and the Health Protection Agency's local and regional services. Further details are given in section 4.2 and will be described in a forthcoming paper.

2.1.10 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The British National Formulary (BNF){5} should be consulted alongside any drug recommendations cited in this guideline and note taken of the indications, contraindications, cautions and product characteristics.

NICE guidelines will normally only make drug recommendations that fall within licensed indications. If a drug is recommended outside of its licensed indication this will be made clear in the guideline. This guideline contains recommendations for prescribing the following, all of which are within current licensed indications:

- ethambutol, for treating active tuberculosis
- isoniazid, for treating both latent and active tuberculosis
- pyrazinamide, for treating active tuberculosis
- rifampicin, for treating both latent and active tuberculosis
- streptomycin, for treating isoniazid mono-resistant active TB
- any glucocorticoid, for treating inflammation associated with active tuberculosis of the meninges or central nervous system (CNS).

The NCC-CC and NICE disclaim any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.2 CG117 [2011]

The Department of Health formally asked NICE to produce a short clinical guideline on interferon-gamma testing for diagnosing latent TB.

The following population subgroups were considered:

- Adults, young people and children at increased risk of infection by Mycobacterium tuberculosis complex (M. tuberculosis, M. africanum, M. bovis), specifically if they:
  - have arrived or returned from high-prevalence countries within the last 5 years
  - were born in high-prevalence countries
  - live with people diagnosed with active TB
  - have close contact with people diagnosed with active TB, for example at school or work
  - are homeless or problem drug users
  - are, or have recently been, in prison.
- Adults and children who are immunocompromised because of:

- prolonged steroid use (equivalent to 15 mg prednisolone daily for at least 1 month)
- TNF-α antagonists such as infliximab and etanercept
- anti-rejection drugs such as cyclosporin, various cytotoxic treatments and some treatments for inflammatory bowel disease, such as azathioprine
- the use of immunosuppressive drugs
- comorbid states affecting the immune system, for example HIV, chronic renal disease, many haematological and solid cancers, and diabetes.

The updated sections of this guideline were developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

2.2.1 Partial update scope

The guideline was developed in accordance with a specified scope, which detailed the remit of the guideline originating from the Department of Health (DH) and specified those aspects of TB to be included and excluded.

Before development of the guideline began, the scope was subjected to stakeholder consultation.

2.2.2 Partial update Guideline Development Group

The GDG met every 6 weeks over a 5-month period from February until June 2010. The group comprised a multidisciplinary team of professionals, patients and carers who were supported by the technical team.

The GDG membership details can be found in appendix K.

Members of the GDG declared any interests in accordance with the NICE guidelines manual. These can be found in appendix K.

2.2.3 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

For the sections published in 2006 literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 30 November 2004 to be considered. For the section on the diagnosis of latent TB published in 2011 literature searches were not

repeated because the development process was only a few months long. The section on diagnosing latent TB includes relevant papers published up until December 2009.

2.3 PH37 [2012]

2.3.1 Introduction

The reviews, primary research, commissioned reports and economic modelling report include full details of the methods used to select the evidence (including search strategies), assess its quality and summarise it.

The minutes of the Programme Development Group (PDG) meetings provide further detail about the Group's interpretation of the evidence and development of the recommendations.

All supporting documents are listed in appendix K and are available at the NICE website.

2.3.2 Guidance development

The stages involved in developing public health programme guidance are:

1. Draft scope released for consultation
2. Stakeholder meeting about the draft scope
3. Stakeholder comments used to revise the scope
4. Final scope and responses to comments published on website
5. Evidence reviews and economic modelling undertaken and submitted to PDG
6. PDG produces draft recommendations
7. Draft guidance (and evidence) released for consultation and for field testing
8. PDG amends recommendations
9. Final guidance published on website
10. Responses to comments published on website

2.3.3 Key questions

The key questions were established as part of the scope. They formed the starting point for the reviews of evidence and were used by the PDG to help develop the recommendations. The overarching questions were:

1. Which interventions are effective and cost effective at identifying and managing TB among hard-to-reach groups?

2. Which case management tools are most effective and cost effective at identifying those who may need support to complete treatment?

3. Which service models and organisational structures are most effective and cost effective at supporting TB diagnosis and treatment for hard-to-reach groups?

4. What factors help or hinder the uptake of TB diagnosis and treatment services by people from hard-to-reach groups. (An example could be the acceptability of different testing modalities.) How can the barriers be overcome?

These questions were made more specific for each review (see reviews for further details).

2.3.46 Reviewing the evidence

Effectiveness reviews

Four reviews were conducted: three effectiveness (including cost effectiveness) reviews and one qualitative review (review 1).

Identifying the evidence

The following databases were searched for all reviews in October 2010:

- ASSIA (Applied and Social Sciences Index and Abstracts)
- BL Direct (British Library)
- British Nursing Index
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- CRD (Centre for Reviews and Dissemination): DARE, HTA, NHS EED (Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment, NHS Economic Evaluations Database)
- CDSR (Cochrane Database of Systematic Reviews)
- Community Abstracts
- Current Contents Connect
- EconLIT
- EMBASE
- ERIC (Educational Resources Information Centre)
- HMIC (Health Management Information Consortium)
- MEDLINE
- MEDLINE In-Process
- PsycINFO
- Sociological Abstracts
- Social Services Abstracts
- SPP (Social Policy and Practice)
- WoS (and conference proceedings) (Web of Science).

The following websites and databases were searched manually for relevant literature:

- Advocacy to Control TB Internationally
- Association of Public Health Observatories
- British Infection Association
- British Thoracic Society
- Centers for Disease Control and Prevention
- Community Abstracts via Oxmill
- Google Scholar
- Health Protection Agency

- National Research Register archive site
- NICE, including the former Health Development Agency and NHS Evidence
- Stop TB Partnership
- TB Alert
- UK Clinical Research Network
- UK Coalition to Stop TB
- World Health Organization
- World Health Organization Global Health Atlas

Selection criteria

Inclusion and exclusion criteria for each review varied and details can be found at the NICE website. However, in general, studies were included if they:

- covered TB services of any kind
- were conducted in an Organisation for Economic Cooperation and Development (OECD) country
- were published in 1990 or later in English
- included data on any hard-to-reach group (that is, any group that was less likely than normal to access healthcare services).

Additional criteria were added for each review as follows:

- Studies were included in review 1 if they presented perceptions of, or attitudes towards, TB services (both qualitative and quantitative views data were included).
- Studies were included in review 2 if they presented quantitative empirical data on identifying TB cases.
- Studies were included in review 3 if they presented quantitative empirical data on managing TB cases.
- Studies were included in review 4 if they presented quantitative empirical data on the design of services to identify or manage TB.

Quality appraisal

Included papers were assessed for methodological rigour and quality using the NICE methodology checklist, as set out in the NICE technical manual 'Methods for the development of NICE public health guidance' (see appendix N). Each study was graded (++, +, –) to reflect the risk of potential bias arising from its design and execution.

Study quality

++ All or most of the checklist criteria have been fulfilled. Where they have not been fulfilled, the conclusions are very unlikely to alter.

+ Some of the checklist criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are unlikely to alter the conclusions.

– Few or no checklist criteria have been fulfilled. The conclusions of the study are likely or very likely to alter.

The evidence was also assessed for its applicability to the areas (populations, settings, interventions) covered by the scope of the guidance. Each evidence

statement concludes with a statement of applicability (directly applicable, partially applicable, not applicable).

Summarising the evidence and making evidence statements

The review data was summarised in evidence tables (see full reviews).

The findings from the reviews were synthesised and used as the basis for a number of evidence statements relating to each key question. The evidence statements were prepared by the external contractors (see appendix N). The statements reflect their judgement of the strength (quality, quantity and consistency) of evidence and its applicability to the populations and settings in the scope.

2.3.5 Cost effectiveness

There was a review of economic evaluations and an economic modelling exercise.

Review of economic evaluations

A range of databases was searched for economic evidence as part of the effectiveness reviews (see above). As a result, several economic evaluations were included in the four reviews.

Economic modelling

An economic model was constructed to incorporate data from the reviews of effectiveness and cost effectiveness. The results are reported in: 'Economic analysis of identifying and managing TB among hard-to-reach groups'.

The model assessed the cost effectiveness of using either a mobile chest

X-ray or enhanced case management – or both – to identify TB among homeless people and prison populations and to manage treatment.

2.3.6 Fieldwork

Fieldwork was carried out to evaluate how relevant and useful NICE's recommendations are for practitioners and how feasible it would be to put them into practice. It was conducted with commissioners and practitioners who are involved in TB services and services for hard-to-reach groups. They included people working in the NHS, local authorities and voluntary sector organisations.

The fieldwork comprised:

- Two focus groups carried out in Manchester and London by Word of Mouth. They involved a range of professionals including commissioners of TB services, TB nurses and drugs service workers.
- Seven individual interviews carried out via telephone by Word of Mouth.
- An online survey.

The fieldwork was commissioned to ensure there was ample geographical coverage. The main issues arising are set out in appendix N under fieldwork findings.

2.3.7 How the PDG formulated the recommendations

At its meetings in 2010 and 2011, the Programme Development Group (PDG) considered the evidence, expert reports and cost effectiveness to determine:

- whether there was sufficient evidence (in terms of strength and applicability) to form a judgement
- where relevant, whether (on balance) the evidence demonstrates that the intervention or programme/activity can be effective or is inconclusive
- where relevant, the typical size of effect (where there is one)
- whether the evidence is applicable to the target groups and context covered by the guidance.

The PDG developed draft recommendations through informal consensus, based on the following criteria:

- Strength (type, quality, quantity and consistency) of the evidence.
- The applicability of the evidence to the populations/settings referred to in the scope.
- Effect size and potential impact on the target population's health.
- Impact on inequalities in health between different groups of the population.
- Equality and diversity legislation.
- Ethical issues and social value judgements.
- Cost effectiveness (for the NHS and other public sector organisations).
- Balance of harms and benefits.
- Ease of implementation and any anticipated changes in practice.

The PDG noted that effectiveness of interventions to identify and manage TB can vary according to the context. For example the background prevalence of TB in a locality.

Where possible, recommendations were linked to an evidence statement(s) (see appendix N for details). Where a recommendation was inferred from the evidence, this was indicated by the reference 'IDE' (inference derived from the evidence).

The draft guidance, including the recommendations, was released for consultation in September 2011. At its meeting in November 2011, the PDG amended the guidance in light of comments from stakeholders and experts and the fieldwork. The guidance was signed off by the NICE Guidance Executive in February 2012.

2.4 NGxxx – clinical sections [2015]

The clinical sections [***] guideline was developed in accordance with the process set out in 'The guidelines manual (2012)'. There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available. In instances where the guidelines manual does not provide advice, additional methods are used and are described below.

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2.4.1 Developing review questions and protocols

The technical team drafted review questions during the scoping precess (see final scope in Appendix B) which were refined and validated by the GDG, using a Population, Intervention, Comparator, Outcome (PICO framework. The GDG and technical team jointly prepared a protocol for each review question (see Appendix C). These protocols formed the starting point for systematic reviews of relevant evidence.

2.4.2 Identifying the evidence

Published evidence was identified by applying systematic search strategies (see Appendix C) to the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards), and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases, the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database.

Where a question was updated directly from CG117 the search strategies used in the CG117 were updated. No date restrictions were placed on the searches for all new questions.

Searches in Embase and Medline were limited to English language and studies in humans. None of the other searches were limited by language of publication (although publications in languages other than English were not reviewed). Validated search filters were used to identify particular study designs, such as RCTs. There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching undertaken of journals not indexed on the databases.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 2nd December 2014.

2.4.3 Reviewing process

2.4.3.1 Study identification

All titles and abstracts identified by the literature searches were sifted for relevance and data were extracted by 1 reviewer. A second reviewer checked a random 10% of sifted out titles and abstracts for accuracy.

When full text articles were ordered and ontained, 1 reviewer examined each articles against the inclusion criteria specified in the review protocol and decided if the study should be included or excluded. All excluded studies and the reason for exclusion and all extracted data from included studies were checked by a second reviewer and the GDG.

2.4.3.2 Data extraction

Basic characteristics of each included study were summarised into standardised evidence tables for each review question (see Appendix D) along with the quality assessment of the evidence. Where outcome data were presented, results were entered as reported in the full-text report of the study. Where data required for analysis were missing, data was imputed as follows;

Table 4: Missing data

Type of missing data	Imputation
standard deviation of the mean change from baseline	imputed using either the baseline standard deviation (SD) from the control group or the SD from a similar group
standard deviation of the point estimate at study	using either the baseline standard deviation

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Type of missing data	Imputation
end	(SD) from the control group or the SD from a similar group.
raw numbers for an outcome	calculated manually from the reported percentage. When a decimal was calculated the number was rounded up if the decimal was over 0.5 and down if below 0.5.

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Quality assessment checklists

For randomised controlled trials, the NICE methodological checklist for RCT's was used for quality assessment of the evidence. For cohort studies, the NICE methodological checklist for cohort study was used for quality assessment. For diagnostic studies, the QUADAS checklist was used for quality assessment. For qualitative studies, the CASP checklist for qualitative research design was used for quality assessment.

Meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For continuous outcomes, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. .

Dichotomous outcomes were presented as odds ratios (ORs), relative risks (RRs) or hazard rations (HRs) with 95% confidence intervals (CIs). Continuous outcomes were presented as mean differences with 95% CIs or SDs, unless data was reported in a form in which this could not occur (for example, as medians and ranges or interquartile ranges).

Software

Data for intervention reviews were analysed using Review Manager 5.1, data for diagnostic reviews was analysed using STATA or R, and WinBUGS was used for network meta-analyses.

Network meta-analysis methods

Network meta-analyses (NMAs) were conducted to simultaneously compare multiple treatments in a single meta-analysis, preserving the randomisation of the included trials in the reviews. This allows all evidence to be combined in a single internally consistent model.

An extensive series of NMAs was undertaken to synthesise evidence on pharmacological treatments to treat latent tuberculosis infection.

Hierarchical Bayesian NMA was performed using the software WinBUGS version 1.4.3. The models were based on the approach and code provided in the NICE Decision Support Unit's Technical Support Documents on evidence synthesis, particularly Technical Support Document 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk/). Model code is provided in Appendix L.

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Dichotomous outcomes

As advised in NICE DSU TSD 2 (Dias et al. 2012a), dichotomous outcomes can be synthesised using 2 alternative models:

- The most straightforward model adopts a binomial likelihood with a logit link function, and generates output on a log-odds scale, with results transformed to odds ratios for presentation.
- An alternative model incorporates data on duration of follow-up in each underlying RCT, assuming a constant rate of events, to estimate the probability of events occurring over time. Again, a binomial likelihood is assumed, but a complementary log–log ('cloglog') link function is used, which results in outputs on a log-hazard scale (transformed into hazard ratios for presentation).

Where differences in follow-up in the underlying evidence were believed or shown to be minor and/or unimportant, the simpler logit-link model was preferred. Where duration of follow-up was believed to have a potential impact on outcomes, both models were explored, and the choice made on the basis of goodness of fit.

The WinBUGS code used for these models is provided in Appendix M.

Zero cells

In datasets containing studies with 'zero cells' (that is, trials in which no events occurred in 1 or more arm), substantial instability was encountered when performing syntheses. To address this problem, a constant of 0.5 was added to all cell counts (effectively adding 0.5 to the numerator and 1 to the denominator of the proportion). The same approach was used to address instability for datasets containing studies with 100% events reported in all arms.

Studies reporting no events in any arms were excluded from NMAs, as they do not provide any information on the relative likelihood of events occurring.

Rate / count outcomes

For rate data (event per unit of person-time), a Poisson model with a log link function was used, to estimate the probability of events occurring over time. These models produce outputs on a log-hazard scale (transformed into hazard ratios for presentation).

Combining dichotomous and rate data

Because both rate data and dichotomous data (with an estimate of follow-up time) can be synthesised on a log-hazard scale, it is possible to combine both types of data in a hybrid model with appropriate likelihoods and link functions for each type of data. This assumes that, regardless of which way the data are reported, the incidence of events has the characteristics of a homogeneous Poisson process. Models of this type were run to combine heterogeneously reported data on the progression of patients from latent tuberculosis infection to active disease.

The WinBUGS code used for the hybrid binomial–cloglog/Poisson–log model is provided in Appendix M.

Prior distributions

Non-informative prior distributions were used in all models. Trial baselines and treatment effects were assigned N(0, 10,000) priors. The between-trial standard

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deviations used in random-effects models were given U(0, 2) priors for dichotomous outcomes. It was felt that this standard deviation was appropriate as the upper limit of 2 represents a huge range of trial-specific treatment effects. This is recommended in NICE DSU Technical Support Document 2.

Running the model

In the first instance, models were run with 50,000 burn-ins and 10,000 iterations. Three separate chains with different initial values were used. If models did not appear to converge well, they were re-run with more burn-ins and/or observations 'thinned' from a large number of posterior samples (for example, every 20th sample of 200,000 could be used to provide 10,000 iterations with minimised autocorrelation).

Syntheses were assessed for any points that significantly deviated from the other data-points and the reasons for any deviate points were investigated.

Goodness of fit

Measures of model fit were scrutinised to assess appropriateness of each model. Particular attention was paid to:

- Total residual deviance: a calculation of the model's ability to predict the individual data-points underlying it. In every iteration of the model sampling procedure, the amount each model-estimated data-point deviates from the observed evidence is calculated, summed and averaged over all iterations. Each data-point should contribute about 1 to the posterior mean deviance; therefore, the total residual deviance of a well-fitting model will be approximately the same as the number of independent data-points in the model
- Deviance information criterion (DIC): an estimate of deviance that is 'penalised' according to the number of parameters in the model (adding parameters to a model should increase its ability to predict known data; however, this may come at the expense of reducing its ability to predict external datasets).
- SD of random-effects term (tau): where a random-effects model is fitted, the width of the inter-study heterogeneity distribution estimated by the model is a reflection of how well the model accounts for heterogeneity in the underlying data. Therefore, while not a measure of goodness of fit per se, it is useful to consider as an indication of how broad a model is required to fit the data. Because inter-study heterogeneity is not modelled in fixed-effects models (that is, tau is assumed to be 0), there is no analogous quantity that can be used to compare different fixed-effects models.

Choice of model (random- versus fixed-effects)

For all syntheses, models were run as both random and fixed effects and model fit measurements were explored to select the most appropriate model for the specific outcome. If either model had clearly superior residual deviance and/or DIC, it was preferred; if there was little to choose between them, fixed-effects models were preferred for reasons of parsimony and interpretability. In practice, this led to a rule where fixed-effects models were preferred unless the corresponding random-effects model had a DIC that was 3 or more lower. Model fit statistics and selection decisions are shown in Appendix L.

An exception to this principle was in instances where there was only 1 study for each link in the network. In this case, no data are available to estimate the random-effects term; therefore, a fixed-effects model was used.

Inconsistency between direct and indirect evidence

As suggested in NICE DSU TSD 4 [Dias et al. 2012c], an 'inconsistency' model was fitted to each dataset on which NMA was undertaken. The outputs of these models were compared with the relevant NMA ('consistency' model) to identify any discrepancies between direct and indirect evidence. In particular, the posterior mean of the residual deviance contribution of within-trial comparisons in each of the 2 models were plotted against each other and visually inspected to see if any inconsistency was suggested (any absolute discrepancy of greater than 0.5 was highlighted and investigated). In practice, few such inconsistencies were seen, and any that occurred were invariably easily explained (in particular, dichotomous syntheses in which zero events were observed in 1 or more trial-arm resulted in high and variable residual deviance estimates). For these reasons (and to avoid unnecessary multiplication of already-numerous results), outputs of the inconsistency models have not been reported. The posterior estimates of effect have, however, been used to show direct evidence in the pairwise relative effect plots relating to dichotomous data (which relied on cloglog or hybrid models that do not lend themselves to simple pairwise frequentist meta-analysis).

More detailed model outputs and a summary of input data for each analysis are available in Appendix L.

2.4.5 GRADE process

The body of evidence identified for each therapy or treatment review question (or part of a review question) was presented in the form of a GRADE evidence profile summarising the quality of the evidence and the findings (pooled relative and absolute effect sizes and associated CIs). Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled risk ratios (RRs), pooled odds ratios (ORs), or mean differences. A random-effects model was used as default.

Where quantitative meta-analysis could not be undertaken, the range of effect sizes reported in the included studies was presented in a GRADE profile.

GRADE was used to assess the quality of evidence for the selected outcomes as specified in ‘The guidelines manual (2012)’. The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of RCTs, or an individual RCT. In the GRADE approach, a body of evidence based on RCTs has an initial quality rating of high, but this may be downgraded to moderate, low or very low if the factors listed above are not addressed adequately. For diagnostic review questions on prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study), and a body of evidence based on such studies would have an initial quality rating of low, which might be downgraded to very low or upgraded to moderate or high, depending on the factors listed above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis or RCT was identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought.

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GRADE profiles for interventional evidence

The quality ratings for each study are reported the study's evidence table and are summarised in the footnotes of each GRADE profile. For this guideline, we inserted footnotes to explain the choice we made while assessing the quality of evidence for each outcomes. These footnotes indicated if we upgraded the evidence level, downgraded the evidence level or left the evidence level unchanged, and gave the rationale for doing this.

The quality of the evidence for each outcome was downgraded where appropriate for the reasons outlined in Table 5.

Table 5: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Example reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about the design or execution of the study, including concealment of allocation, blinding, loss to follow up using intervention checklists in the NICE guidelines manual (2012)
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the statistic, I^2 where ; I^2 < 33% was categorised as no inconsistency, I^2 between 34% and 66% was categorised as serious inconsistency and I^2 > 67% was categorised as very serious inconsistency
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is a minimal important difference. This reflects the confidence in the estimate of effect.
Other considerations	Providing no downgrading for other features has occurred, the quality of the evidence could be upgraded if there was evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect.

Modified GRADE for diagnostic evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework.

Cohort studies within the GRADE approach start at the low quality level due to accepted inherent study design limitations. Within a modified approach, where evidence from cohort studies has been deemed to be the most appropriate source of information to answer a given review question, studies start from a presumption of 'high quality' The same criteria (risk of bias, inconsistency, imprecision and indirectness) were used to downgrade the quality of evidence as detailed in Table 6 below.

Table 6: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Example reasons for downgrading quality

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GRADE criteria	Example reasons for downgrading quality
Risk of bias	This includes limitations in the design or execution of the study, including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating)
Inconsistency	The quality of the evidence was downgraded if there were concerns about Inconsistency of effects across studies: This was assessed using the statistic, I^2 where ; I2 < 33% was categorised as no inconsistency, I^2 between 34% and 66% was categorised as serious inconsistency and I^2 > 67% was categorised as very serious inconsistency (this can reduce the quality rating)
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if there is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is minimal important difference. This reflects the confidence in the estimate of effect.
Other considerations	Providing no downgrading for other features has occurred, the quality of the evidence could be upgraded if confounding variables likely to have reduced the magnitude of an effect.

Modified GRADE for network meta-analyses

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a NMA is still a developing methodology. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when applying modified GRADE to a NMA.

Table 7: Rationale for downgrading quality of evidence in network meta-analyses

GRADE criteria	Example reasons for downgrading quality
Risk of bias	Risk of bias was assessed in accordance with GRADE, as specified in 'The guidelines manual (2012)'. This includes limitations in the design or execution of the study, including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating).
Inconsistency	Evidence of any inconsistency between the direct and indirect estimates of effect was assessed using the residual deviance, deviance information criterion and the statistic tau; outcome was downgraded if tau > 0.5.
Indirectness	The extent to which the available evidence fails to address the specific review question (this can reduce the quality rating). This may be in relation to the setting, population, outcomes, interventions or study designs used in the evidence base. Evidence was only downgraded if this was likely to have an impact on the overall rankings (that is, within smaller networks where there is a lack of evidence or within larger networks in large trials which show large reductions in outcomes).
Imprecision	This is considered to be present when there is uncertainty around the estimate of effect, and reflects the confidence in, or 'credibility' of, the

GRADE criteria	Example reasons for downgrading quality
	estimate of effect. It is assessed based on the overall distribution of the rankings, such that evidence was downgraded if no interventions had rank credible intervals ≤33% of total distribution of comparators.
Other condiderations	

2.4.6 Interpreting the findings

The outcomes prioritised in the review questions and protocols reflect the treatment objectives outlined in each question. The minimum important difference (MID) for both dichotomous and continuous outcomes was decided by looking at appropriate published evidence or under agreement with the GDG following discussion within committee meetings. On the occasion that no published literature on the minimal important difference was identified and the GDG was unable to specify one, a default option was used, for example, in the case of dichotomous outcomes was defined as a relative risk reduction or an increase of 25% or more to be considered clinically important.

For this guideline, the effectiveness of interventions/diagnostic strategies to manage TB has been assessed against a variety of outcomes. The justification for using these outcomes is based on their relevance to people with the condition and the expert consensus opinion of members of the multidisciplinary GDG. When assessing the effectiveness of a particular treatment, information about the effect of that treatment on one or more primary outcomes was sought.

2.4.7 Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. Search strategies are provided in full in Appendix C. In assessing studies for inclusion, population, intervention and comparator criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies; these are shown in Appendix F.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2012; Appendix F). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the guideline. There are two parts of the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table 7).

Table 7: Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness

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Level	Explanation
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

(a) <Insert Note here>

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table 8).

Table 8: Methodological criteria

Level	Criteria
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

(a) <Insert Note here>

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Original health economic modelling was available to support the GDG's decision making for 3 topics in the 2015 update. The GDG prioritised areas in which they felt that original analysis would be particularly informative, on the grounds of uncertainty and variation in current practice and/or the presence of complex trade-offs between benefits, harms and costs of various courses of action. The 3 topics that were selected were: diagnosing latent TB (this work was undertaken by external investigators, Warwick Evidence; see section 3.1), duration of isolation for infectious TB (this work was undertaken by the NICE Internal Clinical Guidelines team; see section of 6.2) and treatment of latent TB (this work was undertaken by external investigators, Imperial College, London; see section 7.2).

In questions for which no published evidence was identified and original analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering potential differences in resource use and cost between the options alongside the results of the review of evidence of clinical effectiveness

2.4.8 Presentation of results

Meta-analyses and reviews

The results of the meta-analyses were presented in a draft chapter sent to the GDG before each meeting. In the meeting, the findings were presented in evidence tables, excluded studies tables, GRADE profiles with forest plots (where available) and evidence statements on the findings. Statements summarising the guideline development group’s interpretation of statements he evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process.

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Presentation of results for network meta-analyses

The results of the network meta-analyses were presented in a number of ways.

- Network diagram, showing availability of evidence. These diagrams have the following features:
  - The size of each node is proportional to total number of participants randomised to receive the treatment in question across the evidence-base.
  - The width of connecting lines is proportional to number of trial-level comparisons available.
  - Where possible, arrowheads are added to the connecting lines to indicate direction of effect in direct pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior ($p<0.05$); outlined arrowheads show direction of trend where effect does not reach statistical significance. It has not been possible to add these for some analyses, as it is not straightforward to quantify direct effects with more complex models.
- Plot of the relative effectiveness, including the results of the NMA of each regimen compared with the reference treatment (for example, see Figure 31) and any direct estimate available for the same comparison.
- Tabulated rank probabilities, giving the probability of each treatment being best (that is, ranked #1) and its median rank with 95% credible interval (CrI). In these outputs, higher ranking always reflect what is best for the patient (for example: higher rates of disease eradication, lower rates of adverse events, and so on).

2.4.9 Agreeing the recommendations

For each review question, recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the guideline development group to agree short clinical and, where appropriate, cost effectiveness evidence statements, which were presented alongside the evidence profiles. The 'Linking evidence to recommendations' (LETR) criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered
- consideration of the clinical benefits and harms
- consideration of net health benefits and resource use
- quality of the evidence
- other considerations (including equalities issues).

In areas where no substantial clinical research evidence was identified, the guideline development group considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on guideline development group consensus in relation to the likely cost effectiveness implications of the recommendations. The guideline development group also identified areas where evidence to answer their review questions was lacking and used this information to formulate recommendations for future research

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations are based on the trade-off between

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the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences. This discussion should help the patient reach a fully informed decision. Terms used within this guideline are:

- 'Offer' – for the vast majority of patients, an intervention will do more good than harm
- 'Do not offer' – the intervention will not be of benefit for most patients
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Towards the end of the guideline development process, the GDG considered all the recommendations and research recommendations that had been drafted previously. The GDG identified 5 high-priority research recommendations.

2.5 NGxxx – public health sections [2015]

The public health sections of this guideline were developed in accordance with the methods set out in 'Methods for the development of NICE public health guidance (third edition) 2012" within the Centre for Clinical Practice process and framework

The minutes of the GDG provide further detail about the GDG interpretation of the evidence and development of the recommendations.

2.6 NGxxx – Service delivery section [2015]

Service delivery guidance aims to provide recommendations on:

- what resources need to be available
- how services should be organised and configured
- the processes that need to be followed to ensure the efficient provision of healthcare interventions of proven clinical and cost effectiveness.

Recommendations on service delivery were developed following NICEs interim guide for developing service guidance 2014 and using review methods from NICEs methods for the development of public health guidance (2012) with the Centre for Clinical Practice process and framework.

2.6.1 Group consistuency

A group of GDG members and additional co-opted experts were tasked with interpreting the presented evidence and drafting recommendations. This 'Service Delivery' group met on 5 occasions and drafted recommendations on the organisation and management of clinical and public health TB services, and subsequently discussed and agreed by the GDG. Any comments suggestions made by the GDG are noted in the relevant LETR tables,

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2.6.21 Scoping

A scoping workshop in January 2014 identified the core approach and a number of key issues for the 'Service Delivery' group to focus on.

The selected key area of focus as outlined in the interim process manual is:

- The best configuration of services to provide high-quality care efficiently and safely

Consideration was given to high level issues such as centralised commissioning and accountability within service delivery. Attention was also given to the different service models that may be required in terms of incidence across areas and regions; and active, latent and drug resistant TB where possible in relation to the main outcomes of interest.

The primary outcomes that were prioritised in the scoping workshop were:

a) diagnosis: specifically 'reducing delayed diagnosis'
b) infection control: specifically 'contact tracing'
c) promoting the uptake of, and improving adherence to, treatment, specifically 'increasing treatment completion'.

2.6.37 Identifying the evidence

The following case study approach to reviewing the evidence was developed during the scoping meeting and agreed with the GDG.

Describe commissioning models, service models, and service structures that are in place in countries, regions and cities that have seen a positive shift in TB incidence and prevalence, in particular how services are commissioned, organised and delivered where possible in relation (but not limited) to:

- reducing diagnostic delay for TB
- improving TB contract tracing
- improving TB treatment completion.

The analysis further differentiated by population sub-group where applicable.

For this section, it was considered important to capture empirical data as well as other information on process, policy and practice. This meant equal weighting was given to identifying evidence via database and non-database sources. A search strategy was used that focused on identifying all relevant papers the outcomes of interest in published research as well as national policy, epidemiology and practice or process evaluations and descriptions in the grey literature for each case study area. This also included a NICE call for evidence (Feb 2014). There were no limits placed on the types of studies or papers to be included.

A mixed method approach to identifying, interrogating and presenting the evidence was taken. It comprises of a systematic literature search to produce three sections of the report:

- Case study profiles of a set of pre-identified cities and countries (UK, New York City, Netherlands, Barcelona and Canada).
- A systematic review of the evidence of the effectiveness of service interventions or models (and aspects of service models) in these case study areas.

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- A systematic review of the evidence of the cost effectiveness of service interventions or models (and aspects of service models) in these case study areas.

A service delivery intervention/model was defined as any service adaptation, such as process changes, change in delivery setting or mode (including staff), and change in structure, accountability or commissioning of a TB service.

The places of interest and outcomes chosen were as specified by the Guideline Development Group (GDG) members of the Service Delivery Group (SDG) during the scoping meeting and subsequent development of the review protocol

Note: The SDG and NICE agreed to use the term ‘under-served’ to denote the high risk groups previously described as ‘hard to reach’ in PH37. The definition from this guideline was adopted to describe these groups therefore, where the term under-served is used, this relates to the definition described above in sub-section 1.1.1 of this chapter and the guideline glossary.

2.6.3.1 Case Studies (Policy and Practice)

The reports, documents and papers were retrieved and examined from the full search results as described in the evidence review (see appendix G7). Inclusion criteria were that the paper reported on policy, practice or TB services in a case study area..

The first objective of the review was to present case studies which describe TB services in the following places:

- UK
- New York City (NYC)
- Canada
- Barcelona
- the Netherlands.

Studies or papers used in the case studies were not critically appraised due to the more discursive nature of this component of the review. Rather than present effectiveness data, the aim here was to build descriptive pictures of the way that TB services are organised (in themselves and in relation to wider health services where possible) in each case area. Papers identified as being of relevance to case studies were grouped by location. Due to the large volume of information available for this section, much of which overlapped, extraction was not undertaken for individual papers. Instead, for each location, a case study extraction sheet was prepared, focusing on audit questions/themes of relevance to the case studies including notification rates and population patterns in TB cases, governance, legislation and accountability, financing and cost of healthcare and TB services, staffing and settings related to TB, and a summary of the TB service delivery model for each case. See appendix G7 chapter 3 for detailed case study information.

The case studies were used to provide an overview for case study areas over the last 10-20 years, and where possible, information on sub-populations that are at increased risk for TB, and the national, regional, and local strategic TB priorities. They also include background information and overviews of their service delivery model, specialist staff and settings relevant to TB in each jurisdiction.

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2.6.3.2 Literature review

Included studies screened in as relevant from the initial search were used to support supplementary searching in three ways:

- Backwards reference harvesting: studies were extracted from the bibliographies of the relevant papers if they are relevant to the scope. Relevant to the scope means TB or tuberculosis is in the title
- Forwards citation searching: the Science Citation Index and the Social Science Citation Index via Web of Science (http://apps.webofknowledge.com) were used to look for later papers citing the references of interest. All citations will be added to Reference Manager
- Related item searching using PubMed via http://www.ncbi.nlm.nih.gov/pubmed/

If there are 1-100 references they will all be downloaded into Reference Manager if they are relevant to the scope. If there are 101 or more references they will be sorted by relevance and then the first 100 will be downloaded into Reference Manager, if they are relevant to the scope.

All studies included in the effectiveness components of the review were critically appraised using relevant checklists from the Methods for the development of NICE public health guidance (Third Edition) and the NICE Interim methods guide for developing service guidance (February 2013).

2.6.3.3 Health economic evidence

The third objective was to identify cost-effective approaches to TB services in the case study areas, with any estimates of cost-effectiveness or cost-impact, in relation to three key outcomes:

- reducing diagnostic delay for TB
- improving TB contract tracing
- improving TB treatment completion.

2.6.4 Expert testimony

'Colloquial evidence' was used to complement the scientific evidence or provide missing information on context. It included evidence about values (including political judgement), practical considerations (resources, professional experience or expertise and habits or traditions) and the interests of specific groups (views of lobbyists and pressure groups). Expert testimony was used when:

- Evidence reviews have uncovered significant gaps in the evidence (or the development team is aware from the outset that the formal evidence is likely to be limited).
- The available evidence conflicts significantly.
- The service delivery group (SDG) wished to seek the views and experiences of specific groups of researchers, practitioners, clients or service users.

Expert testimony was used to provide a range of information about interventions and programmes, including:

- context – for example, the policy or commissioning context
- effectiveness – for example, preliminary results from ongoing interventions or services

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- service design and delivery – for example, detailed information on how a particular service is implemented with different groups of people
- experience – for example, views and experiences of groups of people who have experience of relevant services or practitioners.

The SDG received testimony from a number of experts (lay and professional) in the field on a number of topics:

2.6.5 Data extraction

Studies included in the effectiveness and economic elements of the review were extracted into evidence tables. Data extraction was conducted by one reviewer and checked in detail by a second reviewer. Data were synthesized narratively, and studies were grouped on the basis of outcome.

A further level of synthesis was subsequently undertaken on studies which provided a comparison of one service delivery model/intervention with another service delivery model/intervention, and which provided outcome data that could be linked with the reviews key outcomes: diagnostic delay, treatment completion or contract tracing.

2.6.6 Agreeing recommendations

See section 2.4.9

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The Guideline: Prevention, Diagnosis, Management and Service Organisation

3 Diagnosis

3.1 Diagnosing latent tuberculosis

3.1.1 Clinical introduction

The timely identification and prophylactic treatment of people with latent tuberculosis infection is of public health and clinical importance.

In asymptomatic persons exposure to, and potential infection with, tuberculosis is demonstrated by a positive tuberculin skin test (TST) or a positive blood-based immunological test, specifically an interferon gamma release assay (IGRA). Of those who are infected, the majority will clear the infection. However, in 10–15% infected individuals clinical disease may develop at some point in their lives. If a co-morbidity develops which reduces the immune system, that risk is increased. About half of those who develop the clinical disease will do so within five years of the initial infection. In cases where a long period elapses between infection and development of disease, dormant bacilli are thought to remain in either the lung or other sites, which can 'reactivate' in favourable circumstances for the organism.

Until recently, only Mantoux tests were available to give evidence of exposure. These tuberculin tests had the advantage of being cheap and relatively easy to perform, but suffered from a number of problems. The test results have to be interpreted within a certain timescale, and patients who do not return, or delay returning, will have either no result or a possibly inaccurate one. False positive results can occur because of the sensitising effect on the immune system of either prior BCG vaccination or opportunist environmental mycobacteria. False negative results can occur due to anything reducing immunity, particularly co-infection with HIV but also treatments such as TNF-α antagonists. Extensive tuberculosis (pulmonary or miliary) can itself also temporarily depress the immunity, and can lead to a paradoxically negative Mantoux tests.

More recently, selective immunological tests – IGRAs – have been developed using the tuberculosis antigens 'early secretion antigen target 6′ (ESAT-6) , 'culture filtrate protein 10′ (CFP-10) and tb7.7, which are not present in BCG, and are found in only a few species of environmental mycobacteria. These can be done on either cells or cell products derived from whole blood tests. These tests aim to be more specific by removing false positive results, and to be better correlated with latent infection or dormant organisms.

In order to make appropriate recommendations, review questions were framed according to the following population groups: adults young people and children from high incidence countries, adults, young people and children who had been in contact with individuals with active TB, or immunocompromised individuals. Children were treated as a separate population because they have a less developed immune system than adults, and the mechanism of action of the tests relies on a fully developed immune system.

The key clinical questions considered were:

1. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults, young people and children who are recent arrivals from high prevalence countries?
2. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in children?

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3. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults, young people and children (children considered as a separate population) who have been in close contact with patients with active tuberculosis?
4. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in immunocompromised patients?
5. What is the effectiveness of screening using IGRA for healthcare workers?

3.1.29 Diagnosis of latent tuberculosis: reviews from the 2011 update

3.1.2.10 Methodological introduction [2011]

Because there is now additional evidence available on the use of IGRA, the partial update of CG33 sought to make recommendations on the use of IGRA for diagnosis of latent tuberculosis.

There are 3 IGRAs that have been commercially available for use in the UK: QuantiFERON-TB Gold, QuantiFERON-TB Gold In tube and T-SPOT.TB. QuantiFERON-TB Gold measures the release of interferon-gamma in whole blood in response to stimulation by ESAT-6 and CFP-10 which are not present in BCG vaccine strains or the vast majority of nontuberculous mycobacteria. The In tube version measures ESAT-6, CFP-10 and tb7.7 In the T-SPOT.TB test, individual activated ESAT-6 and CFP-10 specific T-cells are enumerated using ELISPOT methodology.

The key clinical questions considered were:

1. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults, young people and children who are recent arrivals from high prevalence countries? *(note: updated in 2015, so not included here; see section 3.1.3 for updated review)*
2. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in children? *(note: updated in 2015, so not included here; see section 3.1.3 for updated review)*
3. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in adults, young people and children (children considered as a separate population) who have been in close contact with patients with active tuberculosis? *(note: diagnosis in children updated in 2015, so not included here; see section 3.1.3 for updated review)*
4. Which diagnostic strategy is most accurate in diagnosing latent tuberculosis in immunocompromised patients? *(note: updated in 2015, so not included here; see section 3.1.3 for updated review)*
5. What is the effectiveness of screening using IGRA for healthcare workers?

The review protocols are included in appendix K.

A search strategy was used which aimed to identify relevant studies for all the review questions. The following databases were searched: Cochrane database of systematic reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health technology assessment (HTA) database, Medline, Embase, Cinahl, NHS Economic Evaluation database (NHS EED). Trial registers such as Cochrane central register of controlled trials (CENTRAL), UKCRN Portfolio database, current controlled trials, clinicaltrials.gov were searched. Websites of relevant organisations such as World Health Organisation and TB alert were also searched. No methodology search filters or publication date filters were used. A total of 5270

studies were identified for the whole review. After sifting by abstract, 467 studies were selected (n = 56, 70, 69 ,153 and 5 for questions 1 to 5 respectively).

Studies were excluded if they:

- did not compare Mantoux tests with IGRA
- evaluated IGRA based on purified protein derivative
- did not focus on latent TB
- focused on treatment of TB
- focused on non-commercial IGRA or in-house IGRA.

The detailed evidence tables for the included studies and list of excluded papers and reasons for exclusion are given in appendices K.

There were methodological issues with the included papers. For example, active tuberculosis was not always excluded (either through investigation or not reported), there was repeated testing of both Mantoux and IGRAs, the threshold for positive Mantoux tests varied, and it was not clear whether the use of cut-offs was always age appropriate. If identified, these issues were used to downgrade the quality of the evidence in the GRADE profiles (see appendix K).

Diagnostic accuracy studies considered as high quality are those where the index test(s) are compared with a recognised, validated reference standard. Measures of accuracy, when compared with the reference test, such as sensitivity and specificity, can then be determined. However, there is no diagnostic gold standard for identification of latent tuberculosis, with those available providing only indirect and imperfect information. The Mantoux test has been the preferred test in clinical practice for several years but it is not an ideal reference standard; for example, the specificity of the Mantoux test is confounded by BCG vaccination. This implies false-positive results could be seen in this group of people because the Mantoux test is not able to distinguish between individuals who actually have the infection, and those who have been vaccinated with BCG. Because of such concerns about the Mantoux test as a reference standard, other measures of effect such as discordance, concordance and odds ratios are used. These measure the association between the results of the test(s) and the risk of having latent TB, but do not give any information on rates of false positives or negatives.

In addition, the GRADE methodology has not been fully developed for diagnostic studies. A modified form of GRADE was used to assess the quality of evidence found. Standard GRADE profiles for interventions use the following criteria to assess quality of evidence: limitations, inconsistency, imprecision and indirectness. In this review the same criteria were applied. Footnotes have been included to define and describe what the criteria mean in the context in which the studies were analysed. It was not possible to measure imprecision so this has been noted as ‘not measurable’ in the tables. This is because guidance has not yet been developed to address thresholds for imprecision for the measures of effect that were determined. These measures of effect did not appropriately describe the effectiveness of the diagnostic tools. Therefore, the GDG were not asked to agree a pre-defined threshold for imprecision. For questions on children and contact tracing it was possible to pool the ratio of odds ratios and to perform a meta analysis. The ratio of odds ratios is a measure of effect which reflects test performance and provides an approach to evaluating tests in the absence of a reference test. The odds ratio (OR) is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically OR = [sensitivity/(1-specificity)]/[(1-sensitivity)/specificity].

The spreadsheets used to calculate and determine the risk categories as defined by level of exposure to active tuberculosis are given in appendix K.

The main aim of this update was to review diagnosis of latent tuberculosis using tests for which there is no ideal reference standard for comparison. One important objective was to identify appropriate measures of effect to assess the diagnostic utility of the tests. Different approaches were taken to address this objective.

- Discordance and concordance between the IGRA and Mantoux tests were measured in some of the papers. There were few prospective studies to identify participants who would either develop active tuberculosis following a positive test result or stay healthy following a negative test result. These studies are designed to determine positive and negative predictive values. For diagnosis of latent tuberculosis this type of design would give the most accurate prognosis predicting those who will get active tuberculosis and those who would not.
- In other studies the odds of a positive test associated with graded exposure to an active tuberculosis case were measured. In these cases a proxy measure of effect, the ratio of odds ratios could be calculated if figures of positive test results of study participants were clearly stated, and where the exposure status of those participants had been identified. The main disadvantage of this proxy measure is that it fails to identify whether the good performance of a test compared with another is because of either or both. It is impossible therefore to determine the false positive and false negative rates of a particular test.

3.1.2.2 Evidence reviews [2011]

3.1.2.2.1 Diagnosis of latent TB in people who have been in close contact with a person with active TB

Key clinical question

Which diagnostic strategy is most accurate in diagnosing latent TB in people who have been in close contact with a person with active TB?

Evidence review

Of the 27 papers selected:

- Mantoux test thresholds ranged from 5 mm to 30 mm
- 11 papers graded TB exposure, risk and proximal contact and it was possible to pool the results (Anon ; Alvarez-Leon et al. 2009; Brodie et al. 2008; Casas et al. 2009; Diel et al. 2008; Girardi et al. ; Kang et al. 2005; Kik et al. 2009; O'Neal et al. 2009; Topic et al. 2009; Zellweger et al. 2005)
- 16 papers (Adetifa et al. 2007; Alvarez-Leon et al. 2009; Arend et al. 2007; Brodie et al. 2008; Casas et al. 2009; Diel et al. 2009; Hesseling et al. 2009; Kang et al. 2005; Kik et al. 2009; Mirtskhulava et al. 2008; Pai et al. 2005; Porsa et al. 2007; Topic et al. 2009; Tripodi et al. 2009; Vinton et al. 2009; Zellweger et al. 2005) analysed the degree of concordance between Mantoux tests and IGRA
- there were two longitudinal studies (Diel et al. 2008) which followed up participants to investigate the development of active TB.

Table 13 Diagnosing latent TB in people who have been in close contact with a person with active TB.

Study	Results (IGRA versus Mantoux test)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Meta analysis of 11 studies: Alvarez-Leon et al. (2009); Brodie et al. (2008); Casas et al. (2009); Diel et al. (2008); Girardi et al. (2009); Kang et al. (2005); Khanna et al. (2009); Kik et al. (2009); O'Neal et al. (2009); Topic et al. (2009); Zellweger et al. (2005).	Greater than 1 in this case means that positive IGRA was more strongly associated with TB exposure than positive Mantoux test. The overall ROR value was 1.54 (1.08 to 2.19)	Y	Y	N	-	N	Low
Meta analysis of six studies: Brodie et al. (2008), Kang et al. (2005), Khanna et al. (2009), Kik et al. (2009), Topic et al. (2009), Zellweger et al. (2005).	The overall ROR value was 2.07 (1.23 to 3.48). Greater than 1 in this case means that positive IGRA was more strongly associated with TB exposure than positive Mantoux test when BCG vaccination rate was greater than 50%.	Y	Y	N	-	N	Low
Meta analysis of five studies: Alvarez-Leon et al. (2009), Casas et al. (2009), Diel et al. (2008), Girardi et al. (2009), O'Neal et al. (2009)	The overall ROR value was 1.25 (0.94 to 1.67). Greater than 1 in this case means that positive IGRA was more strongly associated with TB exposure than positive Mantoux test when BCG vaccination rate was less than 50%.	Y	Y	N	-	N	Low

Children were considered as a separate population. Outcome was diagnosis of latent TB in contacts from meta-analysis of ROR for IGRA versus Mantoux test. Limitation was the lack of a reference test meant the measures of effect of sensitivity and specificity could not be determined. Inconsistency was that the grading of exposure differed between studies (for example, sleeping proximity, duration of exposure, contact type). Imprecision was not measurable.

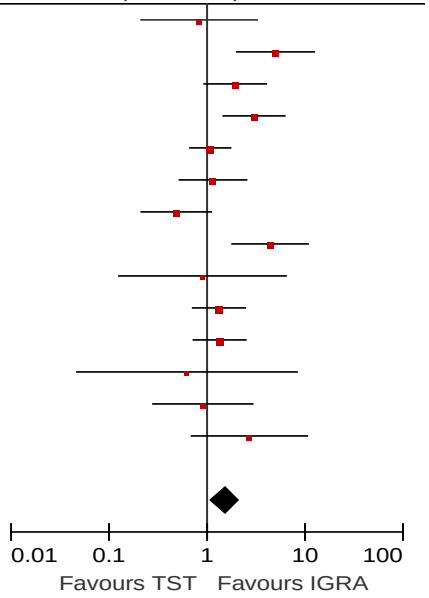
BCG = Bacille Calmette-Guerin. IGRA = interferon gamma release assay; ROR = ratio of odds ratios. TB = tuberculosis

Figure 3 Forest plot of meta-analysis of IGRA and tuberculin skin test results based on high-risk and low-risk exposure to active TB

Study or Subgroup	log[Odds Ratio]	SE	Experimental Total	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Alvarez-Leon etal2009(23)	-0.1839	0.6933	134	134	4.6%	0.83 [0.21, 3.24]
Brodie etal 2008 (479)	1.6094	0.4612	96	96	7.4%	5.00 [2.02, 12.35]
Casas et al 2009(3428)	0.663	0.3696	143	143	9.0%	1.94 [0.94, 4.00]
Casas et al 2009(3428)	1.1048	0.3666	0	0	9.0%	3.02 [1.47, 6.19]
Diel et al 2008 (455)	0.0768	0.2414	601	601	11.5%	1.08 [0.67, 1.73]
Girardi et al 2009(3408)	0.1402	0.4001	115	115	8.4%	1.15 [0.53, 2.52]
Girardi et al 2009(3408)	-0.7222	0.417	0	0	8.1%	0.49 [0.21, 1.10]
Kang et al 2005(1199)	1.4838	0.453	120	120	7.5%	4.41 [1.81, 10.72]
Khanna etal 2009(112)	-0.1076	0.9991	147	126	2.6%	0.90 [0.13, 6.36]
Kik et al 2009(60)	0.2819	0.3135	282	282	10.0%	1.33 [0.72, 2.45]
Kik et al 2009(60)	0.2965	0.3122	0	0	10.1%	1.35 [0.73, 2.48]
O'neal et al 2009 (137)	-0.471	1.3176	61	61	1.6%	0.62 [0.05, 8.26]
Topic et al 2009 (226)	-0.0976	0.5956	54	54	5.6%	0.91 [0.28, 2.91]
Zellweger et al2005(1101)	0.9963	0.6917	91	91	4.6%	2.71 [0.70, 10.51]
Total (95% CI)			**1844**	**1823**	**100.0%**	**1.54 [1.08, 2.19]**

Heterogeneity: Tau² = 0.22; Chi² = 29.36, df = 13 (P = 0.006); I² = 56%

Test for overall effect: Z = 2.40 (P = 0.02)

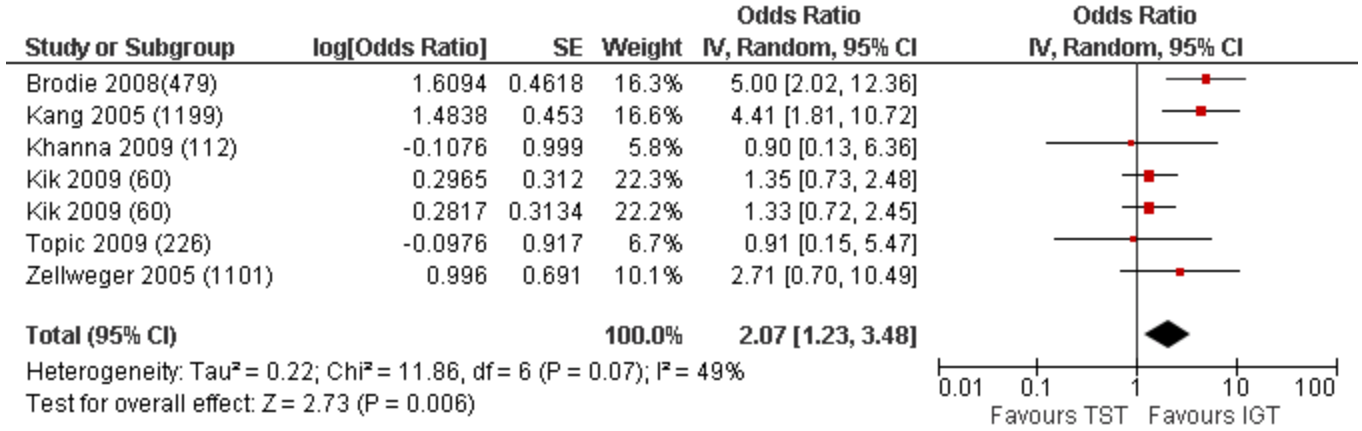


Both OR and ROR in this context, reflect test performance and provide an approach to evaluating tests in the absence of a reference test. OR is a function of test sensitivity and specificity and increases as one or both of these measures increase. Statistically OR= [sensitivity/ (1-specificity)]/ [(1-sensitivity)/specificity].

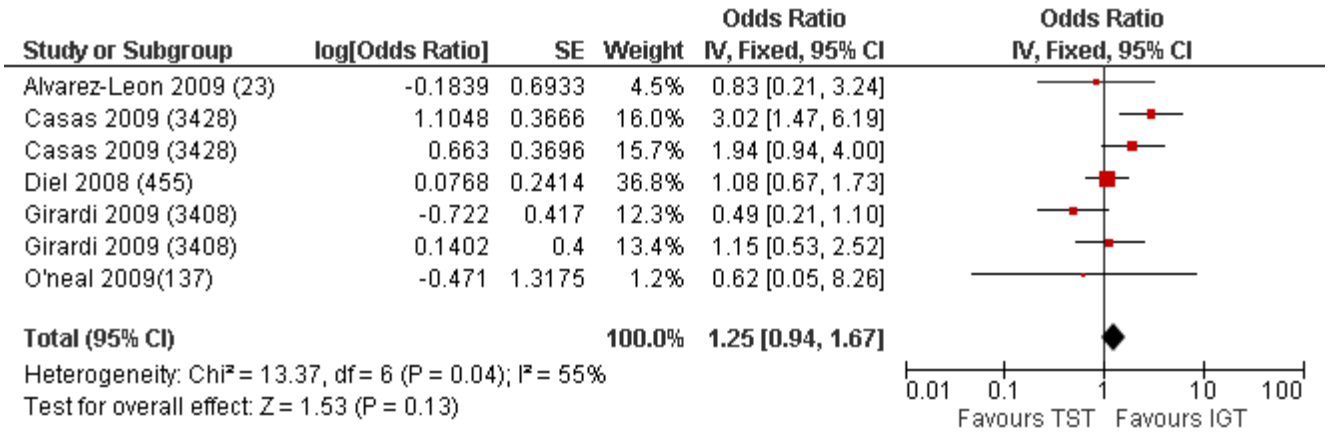
IGRA = interferon gamma release assay. OR = odds ratio. ROR = ratio of odds ratios. TB = tuberculosis. See appendix K for definitions of high and low risk exposure.

Figure 4 Forest plot of meta-analysis of IGRA and tuberculin skin test results based on high-risk and low-risk exposure to active TB stratified by BCG vaccination rates

>50% BCG-vaccinated



<50% BCG-vaccinated



BCG = Bacille Calmette-Guerin. CI = confidence interval. IGRA = interferon gamma release assay. IV = TB = tuberculosis. See appendix K for definitions of high and low risk exposure.

Table 14 Diagnosis of latent TB in people who have been in close contact with a person with active TB (concordance between results).

Study	Results (IGRA versus Mantoux test)	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Sixteen studies[1] (Kang et al. 2756–61;Mirtskhulava et al. 513–9;Tripodi et al. 30;Pai et al. 2746–55;Casas et al. e6686;Topic, Dodig, and Zoricic-Letoja 103–8;Vinton et al. 215–21;Alvarez-Leon et al. 876–83;Hesseling et al. 840–6;Adetifa et al. 122;Brodie et al. 869–74;Porsa, Cheng, and Graviss 714–9;Kik et al. 820–8;Zellweger et al. 1242–7;Arend et al. 618–27;Diel et al. 1010–8)	Overall agreement range was 46.6–94%. Kappa values were 0.11–0.85	Y	N	Y	–	N	Low

Diel et al. (2008)[2]	None of the 25 patients who were IGRA positive and started treatment had developed active TB. Six of 41 patients (14.6%) who were IGRA positive but refused treatment later developed active TB. Five of 219 patients (2.3%) who were Mantoux test positive and were not treated later developed active TB. These patients were followed-up for 2 years	Y	N	N	-	N	Low
Kik et al. (2009)[2]	Positive predictive values were Mantoux test ≥ 10 mm = 3.1%; Mantoux test ≥ 15 mm = 3.8%; QFT = 2.8% ; T-SPOT = 3.3% Negative predictive values were Mantoux test ≥ 10 mm = 100%; Mantoux test ≥ 15 mm = 99.3%; QFT = 98%; T-SPOT = 3.3% These patients were followed-up for median of 1.83 years	Y	N	N	-	N	Low

Children were considered as a separate population.
[1] Outcomes were diagnosis of latent TB in contacts and degree of concordance between Mantoux test and IGRA results.
[2] Outcomes were diagnosis of TB in children and the prognostic value of IGRA in predicting the subsequent development of potential active TB.
Imprecision was not measurable. Limitations were too few participants and too short a follow-up
IGRA = interferon gamma release assay. QFT = QuantiFERON-TB . TB = tuberculosis. TSPOT = T-SPOT.TB

*3.1.2.2.2*1 *Diagnosis of latent TB in healthcare workers*

2 Key clinical question

3 What is the effectiveness of screening using IGRA for healthcare workers?

4 Evidence review

5 Although studies that included healthcare workers had been analysed as part of the
6 contact tracing question (section 5.1.6), the GDG advised that screening in
7 healthcare workers should be specifically looked at. This was because the GDG felt
8 that the scope was open to interpretation with regard to pre-employment screening in
9 the NHS. It was difficult to identify studies that were screening for latent TB in
10 healthcare workers. Good quality studies would have been those which compared
11 participants who had been screened for latent TB and offered treatment as
12 appropriate with those who had not and followed up to determine those who
13 developed active TB. No such studies were identified.

14 Five studies were selected for critical appraisal. Of these:

15 • two (Alvarez-Leon et al. 2009; Harada et al. 2006) looked at existing employees
16 • two (Cummings et al. 2009; Hotta et al. 2007) looked at newly hired workers
17 • two (Harada et al. 2006; Hotta et al. 2007) had participants of whom most were
18 BCG vaccinated
19 • three (Alvarez-Leon et al. 2009; Hotta et al. 2007; Zhao et al. 2009) determined
20 concordance and discordance.

21 The evidence from these screening studies was of very low quality. Most of the
22 issues had already been addressed and analysed in the contact tracing question.
23 Table 21 summarises this evidence.

24 **Table 21 Effectiveness of IGRAs for screening healthcare workers**

Study	BCG vaccination	Healthcare workers	Discordance Positive Mantoux test/negative IGRA	Discordance Negative Mantoux test/positive IGRA
Cummings et al.	93% did not report BCG vaccination	Newly hired	Not determined	Not determined
Harada et al.	95%	Existing employees	Not determined	Not determined
Zhao et al.	Not indicated	Not indicated	25%	0%
Hotta et al.	Most BCG vaccinated	Newly hired	56.5%	0%
Alvarez-Leon et al.	35.1%	Existing employees	4%	2%
BCG = Bacille Calmette-Guerin. IGRA = interferon gamma release assay.				

25 **Evidence statements**

26 Evidence from three low quality papers showed that there was more discordance
27 between positive Mantoux tests/negative IGRA results than negative Mantoux
28 tests/positive IGRA results in 381 healthcare workers. Negative Mantoux
29 tests/positive IGRAs discordance was very low (less than 2%). Some of the

healthcare workers were newly employed. Coverage and timing of BCG vaccination was variable. In two other studies discordance figures were not quantified.

Evidence to recommendations

The GDG agreed that the level of evidence for screening studies was low. It also considered that healthcare workers would fall into the category of people from high prevalence countries or individuals who had had contact with a person with active TB. They made recommendations based on the evidence from those populations. For healthcare workers who were immunocompromised, the recommendations for the immunocompromised group applied.

3.1.2.3 Health economics

3.1.2.3.1 Health economics from the 2006 guideline

A decision model was used to compare the expected cost-effectiveness of four strategies of testing for latent infection in the context of a contact tracing programme in England and Wales. The strategies compared were:

- Mantoux test /IGRA
- Mantoux test followed by IGRA for patients with a positive Mantoux test
- no test (inform and advise only).

It was assumed that treatment followed current policy: with appropriate therapy for people diagnosed with active TB or testing positive for latent infection, and BCG when appropriate for others. The analysis did not compare different types of skin tests or different types of IGRA.

The model is a decision tree, which does not account for the dynamics of disease transmission within the population. Instead, for simplicity, it was assumed that each primary case of active disease is associated with a fixed number of secondary cases. This is probably a reasonable assumption when comparing tests with similar sensitivity, since the absolute difference in false negatives, and hence in opportunities for transmission within the community, will be small. However, estimates of the relative cost effectiveness of contact tracing *per se* are less robust and should be treated with caution.

Various assumptions were made about the epidemiology and likely concordance with testing and treatment programmes. However, it should be noted that these factors will vary with the context of contact tracing. There is also considerable uncertainty over the relative accuracy of the Mantoux test and IGRA, as well as over some of the other model parameters. Whenever possible input parameters and assumptions were based on empirical evidence, but some key parameters were estimated by the health economist and GDG.

Cost-effectiveness of testing strategies in contact tracing

The basecase economic analysis suggests that the two-stage strategy (Mantoux test /IGRA) is within the range usually considered 'cost-effective', at around £26,000 per quality-adjusted life-year (QALY) gained. Compared with this, IGRA is not cost-effective (over £150,000 per QALY gained). Mantoux test is both less effective and more expensive than all of the other options (it is 'dominated').

Variation in optimal strategy within the context of contact tracing

The results of the economic analysis were highly dependent on the context of the contact tracing scheme – with a higher-risk cohort of contacts, the expected benefits of early diagnosis of active cases, treatment of latent infection, and vaccination will be greater. Below a prevalence of about 10% none of the testing strategies is cost-effective. At intermediate levels of prevalence (between about 10% and 40%), the two-stage Mantoux test /IGRA strategy is cost effective. Above 40% IGRA on its own is the most cost-effective option.

Table 25: Cost-effectiveness of diagnostic strategies

Prevalence of infection	Strategy	Cost (£)	Effect (QALYs lost)	ICER[6] (£ per QALY gained)
0	No test	£31	0.00409	–
	Mantoux test/IGRA	£58	0.00394	£178,835
	IGRA	£102	0.00394	(Dominated)
	Mantoux test	£139	0.00404	(Dominated)
10%	No test	£191	0.02533	–
	Mantoux test/IGRA	£240	0.02323	£23,351
	IGRA	£282	0.02290	£126,813
	Mantoux test	£314	0.02310	(Dominated)
20%	No test	£351	0.04658	–
	Mantoux test/IGRA	£423	0.04252	£17,575
	IGRA	£463	0.04185	£60,073
	Mantoux test	£489	0.04217	(Dominated)
30%	No test	£512	0.06782	–
	Mantoux test/IGRA	£605	0.06182	£15,553
	IGRA	£643	0.06081	£38,081
	Mantoux test	£664	0.06123	(Dominated)
40%	No test	£672	0.08907	–
	Mantoux test/IGRA	£788	0.08111	£14,522
	IGRA	£824	0.07976	£27,132
	Mantoux test	£838	0.08029	(Dominated)
50%	No test	£832	0.11031	–
	Mantoux test/IGRA	£970	0.10040	£13,898
	IGRA	£1,005	0.09872	£20,578
	Mantoux test	£1,013	0.09936	(Dominated)

[6] ICER = incremental cost-effectiveness ratio

Uncertainty over optimal testing strategy for contact tracing

The results of the economic analysis were subject to a high degree of uncertainty. The results were very sensitive to assumptions about the relative accuracy of the two types of test, the risk of current and future TB in the cohort, the level of transmission to the wider population, and also to the expected net benefit of avoiding each active case of TB.

3.1.2.3.27 Partial update health economics introduction [2011]

The following sections outline the updated modelling for two populations identified in the scope: adult contacts (including health care workers) and screening people from high prevalence countries. However, because of an absence of evidence, no cost-effectiveness analysis was conducted for all child and young people populations. Because of an absence of information no new distinct analysis was conducted for screening new NHS employees and the immunocompromised population. For children, the almost complete absence of sensitivity and specificity information and quality of life data meant that a useful analysis could not be produced. For the two remaining adult populations the results of the other two analyses will be extrapolated to these situations

A search for cost-effectiveness studies identified five relevant papers that examined the use of IGRA in screening people from high prevalence countries with suspected latent tuberculosis infection, and one relevant paper that examined the use of IGRA in the adult contacts and healthcare workers contacts with suspected latent tuberculosis infection. The papers were reviewed with quality checklists to assess their applicability and limitations. None of the papers were considered applicable to the decision problem either because they were not based in the UK or did not include consideration of quality of life. However cost-effectiveness papers were used to explore approaches to modelling strategies and to inform the structure of the model.

A decision model based on the previous guideline was used to compare the expected cost effectiveness of four strategies of testing for latent infection in both adult (aged more than 18 years) populations described above. The strategies compared were:

- Mantoux test
- IGRA
- Mantoux test followed by IGRA
- no test.

In the model, treatment follows current policy; with appropriate therapy for people diagnosed with active and latent TB. The analysis did not compare different types of skin tests or IGRAs because this was outside the scope of this guideline.

The key areas that were updated were the test accuracies and the relevant costs. All costs were updated to current prices and were validated by the GDG. The test accuracies were based on published reviews which calculated sensitivities and specificities again after validation by the GDG.

The assumptions made in the initial guideline were still applicable unless stated otherwise. Whenever possible, input parameters and assumptions were based on empirical evidence, but some key parameters were estimated by the health economist and GDG. The model considers the quality-adjusted life years (QALYs) lost because of infection, adverse events and developing TB. Therefore, the interventions with the smallest QALY loss are the most effective. Throughout the analysis incremental cost-effectiveness ratios (ICERs) will be compared with a

common base line (usually no test) and net monetary benefits will be calculated. Net monetary benefit quantifies which treatment option provides the greatest health benefit for a given threshold. A threshold of £20,000 per QALY gained was used in this analysis. Probabilistic sensitivity analysis was considered, however some of the estimates of the means of variables were assumptions and it was therefore considered more instructive to do a series of one way sensitivity analysis rather than a probabilistic sensitivity analysis.

For each population details were given on the source of the new test accuracy data with base-case results and sensitivity analyses.

3.1.2.3.3 Health economics – contact tracing for healthcare workers (this section also relates to the diagnosis of latent TB in people who have been in close contact with a person with active TB) [2011]

The economic model used the same structure, costs and health-related quality of life values as those in the model for adults from high prevalence countries. However, the difference is in the estimates of the test accuracy and the prevalence of latent TB infection in this cohort. The test accuracy was based on Girardi et al. (2009) and Diel et al. (2010). The baseline prevalence used was 20%.

The model assumed the treatment regimen was the same as for people from high prevalence countries and that diagnosing and screening for latent TB was done in an outpatient setting.

The base case analysis for this population is shown in table 8.

Table 8: Cost-effectiveness of testing strategies for contacts

Strategy	**Cost (£)**	**Effect (QALY loss)**	**ICER compared with no test (£)**	**Net monetary benefit (£20,000 per QALY gained)**
Girardi et al. (2009)				
No test	380	9.9393	-	-
Mantoux test/IGRA	476	9.9473	12,037	£64
IGRA	531	9.9483	16,833	£29
Mantoux test	604	9.9484	24,637	-£42
Diel et al. (2010)				
No test	380	9.9393	-	-
Mantoux test/IGRA	445	9.9435	15,174	£21
IGRA	515	9.9473	16,244	£25
Mantoux test	567	9.9447	Dominated	Dominated
ICER = incremental cost-effectiveness ratio. IGRA = interferon gamma test. QALY = quality-adjusted life year.				

These results indicate that Mantoux test/IGRA and IGRA alone are both cost-effective testing options and that depending on the test accuracies used either option could be the optimum choice.

Table 9 presents sensitivity analysis on the prevalence of latent TB in this conctacts population. The transformation rate did not appear to be a major variable in the model. Results are reported as net monetary benefits at the £20,000 per QALY gained threshold.

Table 9: Net monetary benefits at £20,000 per QALY gained for different prevalence rates and test accuracy sources for contact tracing

Prevalence	Mantoux test/IGRA	IGRA	Mantoux test
Girardi et al. (2009)			
0.01	−36	−97	Dominated
0.05	−15	−71	Dominated
0.1	11	−37	Dominated
0.15	38	−4	−83
0.2	64	29	−42
0.25	90	62	−1
0.3	116	95	40
Diel et al. (2010)			
0.01	−31	−85	Dominated
0.05	−20	−61	Dominated
0.1	−7	−33	Dominated
0.15	7	−3	Dominated
0.2	21	25	Dominated
0.25	34	54	Dominated
0.3	48	83	Dominated

At £20,000 per QALY gained the prevalence has to be over 10% for testing to be cost effective. At a £30,000 per QALY gained threshold the lowest prevalence rate that testing remains cost effective at is 6%. In the contacts model, the transformation from latent to active TB was implemented by a relative risk (please see 2006 guideline appendix K for more details) the net monetary results at £20,000 per QALY gained are presented in table 10.

Table 10: Net monetary benefits at £20,000 per QALYgained for different transformation rates and test accuracy sources for contact tracing

Latent TB to active TB	Mantoux test/IGRA	IGRA	Mantoux test
Girardi et al. (2009)			
0	18	−23	−96
1	29	−10	−82
2	41	3	−69
3	52	16	−56
4	64	29	−42
5	75	42	−29
6	87	55	−16
Diel et al. (2010)			
0	−3	−20	Dominated
1	3	−9	Dominated
2	9	2	Dominated
3	15	14	Dominated

4	21	25	Dominated
5	27	36	Dominated
6	32	48	Dominated

These results indicate that if the risk of latent TB becoming active is high then the cost-effectiveness results improve for all the options.

These results also indicate that IGRA or Mantoux test/IGRA could be the optimum choice but that it is highly dependent on the prevalence of latent TB in the population.

3.1.2.45 Evidence statements [2011]

Low quality evidence from 11 studies with 1844 participants showed that positive IGRAs were more strongly associated with increasing TB exposure than positive Mantoux tests (ROR = 1.54 [95% CI 1.08 to 2.19]). In those studies with less that 50% BCG-vaccinated patients the ratio of odds ratio was 1.25 (95% CI 0.94 to 1.67), whereas in those with over 50% BCG-vaccinated patients it was 2.07 (95% CI 1.23 to 3.48).

Low quality evidence from 16 studies showed that the degree of concordance between Mantoux test and IGRA results, as measured by kappa values, was between 0.11 and 0.85.

Low quality evidence from one study showed IGRAs were more likely to detect progression to active TB than Mantoux tests over a 2-year period. Positive predictive values were 14.6% and 2.3% respectively.

Low quality evidence from one study following up 339 immigrant contacts for a median of 1.83 years showed that IGRAs and Mantoux tests were similar in detecting progression to active TB. Positive predictive values were 3.1% and 3.8% for Mantoux test thresholds of 10 mm and 15 mm and 2.8% and 3.3% for QFT and T-SPOT. Negative predictive values were 100%, 99.3%, 98% and 98.3% respectively.

Test results and exposure to tuberculosis

In a UK study of healthy adults in a contact tracing clinic, IGRA (ESAT-6 ELISPOT assay) results had a strong positive relationship with increasing intensity of contact exposure (OR 9.0 per unit increase in exposure, 95%CI 2.6 to 31.6, p=0.001), whereas Mantoux test results had a weaker relationship with exposure (OR 1.9, 95%CI 1.0 to 3.5, p=0.05). **(2)**

In contacts of index cases in the Gambia, with increasing M. tuberculosis exposure, the percentage of participants who were tuberculin positive and interferon gamma test (ESAT-6/CFP-10 ELISPOT assay) negative increased from 11% of those sleeping in a different house from the index case to 32% of those sleeping in the same room (p<0.001). **(3)**

In contacts of an index case on an Italian maternity unit, the odds for a test result being positive for each increase across four stratified exposure groups (from no discernible contact to household contacts) increased by 1.93 (95%CI 1.11 to 3.35, p=0.020) for the IGRA (ESAT-6/CFP-10 ELISPOT assay) but there was no significant correlation for the Mantoux test. **(3)**

In Korea where BCG vaccination is mandatory,{15} a study found that the odds of a positive test result per unit increase in exposure across four groups, increased by a factor of 5.31 (95%CI 3.62 to 7.79) for the IGRA (QuantiFERON-TB Gold) and by a factor of 1.52 (95%CI 1.2 to 1.91) for the Mantoux test (p<0.001). **(2)**

Test results and BCG status

Healthy adults in a contact tracing clinic in the UK, had IGRA (ESAT-6 ELISPOT assay) results which were not correlated with BCG vaccination status whereas Mantoux test results were significantly more likely to be positive in BCG vaccinated contacts (OR 12.1, 95%CI 1.3 to 115.7, p=0.03). **(2)**

In a UK study of healthy household contacts and healthy unexposed controls, ESAT-6 peptide-specific interferon-gamma-secreting cells were detected in 85% of the healthy household contacts who were tuberculin positive. None of the healthy control subjects without a history of TB exposure, responded to this IGRA even though all unexposed control subjects were BCG vaccinated. **(3)**

Mantoux test negative Australian born medical students (or those born in another low prevalence country), with no prior BCG, and no known exposure to TB, were BCG vaccinated and then tested again at five months. ESAT-6 stimulated interferon-gamma levels (using ESAT-6 QuantiFERON) were very low or undetectable in all students both before and after BCG vaccination. Of these students, 46% had Mantoux test responses of 0 to 4 mm and 54% had responses of ≥5 mm. Thirteen percent had Mantoux test results of ≥10 mm. Under current Australian guidelines, one student with a 16 mm result was defined as having a Mantoux tes result suggestive of M. tuberculosis infection. **(3)**

High school contacts in a TB outbreak in Denmark who had high exposure to an index case and were not BCG vaccinated, had agreement between Mantoux test and IGRA (QuantiFERON-TB Gold) results of 93% (95%CI 86 to 100%). This was 95% (95%CI 88 to 102%) in the low exposure group and an overall agreement between the two tests of 94% (95%CI 89 to 99%) in all subjects tested. The kappa value was 0.866, indicating high agreement between the two tests. **(3)**

In an Italian study of contacts of an index case on a maternity unit, IGRA (ESAT-6/CFP-10 ELISPOT assay) results were independent of BCG vaccination status. **(3)**

IGRAs were prescribed by hospital physicians for inpatients or outpatients in an Italian study with no influence from the study investigators. After excluding indeterminate results, the agreement between IGRA (QuantiFERON-TB Gold) and Mantoux test results was significantly lower among BCG-vaccinated individuals than in non-vaccinated individuals (41.5% vs. 80.3%, p<0.0001). **(3)**

In a study of healthcare workers conducted in India (where nontuberculous mycobacteria are highly prevalent), previous BCG vaccination was not associated with Mantoux test or IGRA (QuantiFERON-TB Gold) positivity. **(3)**

Indeterminate test results

An Italian study found that indeterminate IGRA results (QuantiFERON-TB Gold) were significantly over-represented in patients with a negative Mantoux test (28.6% vs. 6.6% in tuberculin positive patients, p<0.001) and were more frequent in patients receiving immunosuppressive therapies than in those who were not receiving such treatments (OR 3.35, 95%CI 1.84 to 6.08, p<0.0001). Immunosuppressive therapy was defined as cancer chemotherapy, systemic steroids, or anti-tumour necrosis factor alfa agents at the time of testing. **(3)**

Evidence to recommendations from the 2006 guideline

IGRAs showed little evidence of being affected by prior BCG vaccination, and showed stronger correlation with exposure categories than did Mantoux test. This

was shown in low prevalence groups, in household contacts, and in outbreak situations. The specificity of IGRAs seemed better, and there was less potential for false positive results. It is not possible to determine, for either a Mantoux test or IGRA, the rate of false negative results. Some people with false negative results will go on to develop active TB and thus reduce the cost-effectiveness of vaccination and treatment of latent TB infection.

Prospective studies in people with latent TB (as judged by positive IGRAs) found at TB contact tracing and new entrant screening, have not yet been performed to find what proportion of such persons went on to develop clinical disease.

Economic modelling was undertaken with various strategies from no action to a two-step strategy with either a Mantoux test followed by interferon-gamma testing, or serial IGRAs. Of these options, the model provided most support, on grounds of cost-effectiveness, for a two-step approach with an initial Mantoux test, followed by an IGRA to confirm positivity. The GDG members also supported this because of clinical utility and feasibility.

3.1.2.5 Evidence to recommendations [2011]

The population included healthcare workers who were in contact with people with active TB and non healthcare workers, who by way of residence, had been in close contact with a person with active TB. The GDG was presented with evidence showing the meta-analysis of ROR for comparing IGRAs with Mantoux tests. This was stratified by percentage BCG vaccination. When adjusted for BCG vaccination, IGRAs showed a better ROR than Mantoux tests. The GDG felt that although IGRAs seemed better from ROR, the evidence was of poor quality and that recommendations should ideally be based on longitudinal studies that aimed to determine positive and negative predictive values of a person developing active TB.

The health economic analysis for contacts was extrapolated to this population. This analysis indicated that there was uncertainty over which testing strategy was the optimal choice. Therefore, the GDG considered that both tests should be offered and that depending on operational issues, the most appropriate should be used.

In the studies evaluated, IGRA show a stronger correlation with exposure than Mantoux tests. Much of the discordance between a positive Mantoux test and a negative IGRA can be accounted for by prior BCG vaccination. The GDG agreed that in the absence of good quality longitudinal studies the relative benefit of IGRA over Mantoux test in determining the need for treatment of latent infection is not certain. However they made recommendations in populations where they considered IGRA to be of clear benefit especially in cases where IGRA would reduce the uncertain diagnosis of Mantoux tests.

No further evidence was reviewed for other groups such as prisoners/prison staff and nursing homes. However, the GDG felt that the tests should perform as with any other adults.

3.1.3 Diagnosis of latent tuberculosis: reviews from the 2015 update

3.1.3.1 Review questions [2015]

Of the five reviews conducted for the 2011 guideline, most were updated as follows:

Table 11: Status of review questions from 2011

2011 review question	Update status
Which diagnostic strategy is most accurate in diagnosing latent TB in adults, young people and children who are recent arrivals from high prevalence countries?	Full update
Which diagnostic strategy is most accurate in diagnosing latent TB in children?	Full update
Which diagnostic strategy is most accurate in diagnosing latent TB in adults, young people and children (children considered as a separate population) who have been in close contact with patients with active TB?	Partial update – children and young people now included in 2nd question above
Which diagnostic strategy is most accurate in diagnosing latent TB in immunocompromised patients?	Full update
What is the effectiveness of screening using IGRA for healthcare workers?	Not updated

The review questions used in the 2015 update are as follows:

1. Which diagnostic strategy is most clinically and cost-effective in accurately identifying latent TB in children?
2. Which diagnostic strategy is most clinically and cost-effective in accurately identifying latent TB in people who are immunocompromised or at risk of immunosuppression?
3. Which diagnostic strategy is most clinically and cost-effective in accurately identifying latent TB in people who are recent arrivals from countries with a high incidence of TB?

3.1.3.2 Evidence review [2015]

The reviews for these questions were developed externally, by Warwick Evidence, under the NIHR's Technology Assessment Review (TAR) contract. Members of the Warwick Evidence team attended GDG meetings to discuss protocols for reviews and health economic analysis, and to present preliminary and final results. A pre-peer-review version of the TAR is available in appendix H; note that this document will undergo external peer review before it is published in the *Health Technology Assessment* series.

The bibliographic database search strategies focussed on the diagnosis of latent tuberculosis infection using IGRAs compared to other methods, and were limited to articles in English that had been published since the equivalent searches were performed for NICE clinical guideline CG117 (7 – 14 December 2009; Appendix 1). The searches automatically picked up comparisons in performance between IGRAs and TSTs, therefore it was not necessary to search independently for comparator technologies (that is, TSTs).

The search strategy comprised the following main elements:

- searching of electronic bibliographic databases;
- contact with experts in the field;
- scrutiny of references of included studies and relevant systematic reviews; and
- screening of manufacturers' and other relevant websites.

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The following bibliographic databases were searched:

MEDLINE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); Cochrane Library incorporating Cochrane Database of Systematic Reviews, CENTRAL, DARE and HTA databases (Wiley); Science Citation Index and Conference Proceedings (Web of Science); and Medion. ClinicalTrials.gov and WHO ICTRP were searched for ongoing and recently completed trials.

Specific conference proceedings, selected with input from a clinical expert, were checked for the last five years. The online resources of relevant organisations were searched.

Citation searches of included studies were undertaken using the Web of Science and Scopus citation search facilities. The reference lists of included studies and relevant systematic reviews were checked. Included papers were checked for errata using PubMed. Identified references were downloaded to bibliographic management software (Endnote X7).

Studies were included if they met the following criteria:

- they were primary studies evaluating and comparing head-to-head effectiveness of commercially available approaches/tests used for identifying people with latent tuberculosis infection:
  - IGRAs (e.g. QuantiFERON-TB Gold In Tube (QFT-G-IT) [old version: QuantiFERON-TB Gold (QFT-G)] or T-SPOT.TB);
  - TST (i.e., Mantoux test).
- the population included the following:
  - children (both genders, aged less than 18 years, immunocompetent);
  - people (both genders, any age) who are immunocompromised or at risk from immunosuppression (e.g. transplant recipients or those with HIV, renal disease, diabetes, liver disease, haematological disease, cancer, autoimmune disease, or who are on or about to start anti-TNF-α treatment, steroids, or cyclosporins);
  - people (both genders, any age, immunocompetent) who have recently arrived from regions with a high incidence/prevalence of TB (countries/territories with an estimated incidence rate of 40 per 100,000 or greater e.g. those in Africa, Central/South America, Eastern Europe, and Asia).
- they included comparisons of test results with the following construct validity measures (as a proxy for the outcomes of interest):
  - progression to active tuberculosis disease;
  - exposure to *M. tuberculosis*, defined by proximity, duration, geographic location, or dose-response gradient;
  - people at low risk of M. tuberculosis infection or healthy populations.

Studies were excluded if they met any of the following criteria:

- did not compare IGRAs to TSTs with regards to the pre-specified construct validity measures (that is, incidence of active tuberculosis disease, exposure to *M. tuberculosis*, defined by proximity, duration, geographic location, or dose-response gradient);
- did not compare the accuracy of tests (IGRAs with TSTs) for the identification of people with latent tuberculosis infection in head-to-head comparisons;
- studies (involving, though not limited to, children, recently arrived immigrants or immunocompromised people) which do not report subgroup data separately for each relevant population;
- compared IGRAs to eachother (e.g. QFT-G-IT compared to T-SPOT.TB) in identifying people with latent tuberculosis infection;
- studies which have applied non-commercial IGRAs, in-house IGRAs, older generation IGRAs (e.g., PPD-based 1st generation QuantiFERON-TB), or tests unavailable in UK;

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- the study assessed the effects of antituberculosis treatment on IGRA or TST results;
- have evaluated and/or compared reproducibility of tests (that is, test and retest comparability) for identifying latent tuberculosis infection;
- do not focus specifically on latent tuberculosis infection (e.g. studies in which the presence of culture-positive tuberculosis is used to estimate sensitivity; in these, 'active tuberculosis' is assumed as the reference standard for the 'true presence' of latent tuberculosis infection – given that active disease and latent infection are two clinically and immunologically distinct forms of tuberculosis, this assumption is problematic);
- use serial testing of IGRAs or TSTs to detect latent tuberculosis infection;
- focus on a specific biomarker (e.g. IP-10);
- are systematic/narrative reviews, meta-analyses, case reports, case-series, abstracts, commentaries, letters or editorials.

For each review question, evidence was extracted into evidence tables and critically appraised. A full report of the reviews – including a full description of the methodology, the search strategies, evidence synthesis and health economic analysis can be found in Appendix H.

3.1.3.37 Health economic evidence

A systematic review was undertaken by Warwick Evidence to identify literature describing existing cost-effectiveness analyses. The bibliographic database search strategies were the same as those run for the clinical effectiveness review. Searches were limited to articles in English and included articles that have been added to databases since the health economics searches for the equivalent questions in CG117 were run (5–6 January 2010).

The literature search identified 3057 records. On the basis of title and abstract, 3032 records were excluded. The remaining 25 records were included for full-text screening. A further 15 articles were excluded at the full-text stage, leaving 10 studies estimating the cost-effectiveness of IGRAs compared with TST in diagnosing people who are at high risk of LTBI.

The majority of these models were in the immunocompromised population. Most used decision-tree structures with Markov nodes to simulate a cohort of people being tested for LTBI. A critical appraisal of the included studies showed that all performed well in terms of defining the decision problem, including the study perspective, outlining the choice of comparators, presenting an illustrative model structure and providing a clear outline of the assumptions. However, the majority of the studies stated the location of the study but not the setting of the analysis and this may limit the generalisability of the results. The main outcome measure in most of the included studies was QALYs, but many did not elaborate on the descriptive tool used to value health states. The perspective of the analysis was stated in all studies, but the resource use and costs reported did not reflect the viewpoint of the analysis in some studies. Finally, all models explored uncertainty around key model input parameters, but no attempt was made to explore methodological generalisability or structural uncertainty. Other concerns relate to the derivation of prevalence, test accuracy and transition probabilities; most studies have not elaborated on these statistical/pre-model analyses. A detailed summary of these included studies is included in Table 26 of Appendix H.

Original health economic model

Subsequent to the clinical and health economic systematic reviews, an original individual patient simulation was developed by Warwick Evidence to analyse the cost-effectiveness of either:

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- Tuberculin skin test (TST) alone (5 mm and 10 mm induration thresholds simulated separately)
- Interferon-gamma release assay (IGRA) alone (3 tests considered – QFT-GIT, QFT-G or T-SPOT)
- Sequential TST and IGRA

for the detection of TB in 3 population subgroups considered to have high risk of progression to active TB: immunocompetent children, newly arrived migrants from high TB prevalence countries and people who are immunocompromised. The model explores the cost effectiveness of these strategies on the assumption of an intention to test, and therefore did not compare the different strategies with no testing. The analysis followed the NICE reference case, using an NHS/PSS perspective for costs and discounting costs and benefits at 3.5% per annum. The diagnostic testing strategies were mapped out using a decision tree that captures the relevant events and associated costs, benefits and harms, across the diagnostic pathway for each test and population. The analysis is linked to a disease progression model covering the following states:

- Active TB
- LTBI – treated for LTBI
- LTBI – untreated
- No TB/LTBI – treated for LTBI
- No TB/LTBI - untreated

Patients in the active TB state cause secondary infections of LTBI that may progress over time to active TB. As the model is run, any new cases of LTBI infection generated are then fed into the disease progression model, where costs and QALYs are calculated based on the time spent in each state. The model has a time horizon of 100 years (applied because, beyond this point, discounting of costs and QALYs means further events would have minimal impact on the decision outcome).

Parameter estimates for natural history and diagnostic accuracy variables were taken from the systematic review of clinical evidence summarised in section 3.1.3.2, with the exception of those studies with a high incidence of active TB. For the diagnostic accuracy data, see table 12 below. This was done to better approximate the epidemiology of TB in England and Wales. The model incorporates the cost of diagnostic testing, the cost of active TB treatment, and the costs of LTBI treatment including adverse events from hepatoxicity.

Table 12 Diagnosis of latent TB: diagnostic accuracy variables from clinical effectiveness reviews

	Sensitivity, % (95% credible interval)	**Specificity, % (95% credible interval)**
Children		
TST (≥ 5mm)	72.80 (60.59 – 72.94)	49.03 (47.96 – 50.08)
TST (≥ 10mm)	53.51 (38.21 – 67.69)	74.81 (34.34 – 76.18)
QFT-GIT	68.84 (58.56 – 78.20)	61.03 (60.30 – 61.76)
T-SPOT.TB	50.00 (2.45 – 97.64)	77.58 (67.38 – 86.40)
Immunocompromised		
TST (≥ 5mm)	32.42 (11.19 – 58.48)	74.22 (72.88 – 75.57)
TST (≥ 10mm)	16.82 (2.52 – 38.99)	83.97 (78.99 – 88.31)
QFT-GIT	55.48 (24.73 – 83.73)	82.27 (80.52 – 83.96)
T-SPOT.TB	66.65 (35.17 – 0.9144)	68.46 (63.46 – 73.37)
Recently arrived		
TST (≥ 5mm)	93.56 (77.86 – 99.77)	50.11 (47.90 – 52.29)

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QFT-GIT	59.15 (35.84 – 81.42)	79.29 (77.80 – 80.73)
T-SPOT.TB	70.01 (39.78 – 92.42)	39.92 (34.39 – 45.54)

A probabilistic sensitivity analysis was undertaken, with results presented as mean ICERs and diagnostic errors avoided for each strategy.

The results show that, in children, TST (≥ 5 mm) is marginally more effective than the QFT-GIT alone strategy, with an ICER of approximately £11,255 per QALY, and has a 27% probability of being the most cost-effective strategy at £20,000 per QALY. The most effective strategy is TST (≥ 5 mm) negative followed by QFT-GIT, which is the most cost-effective strategy in 32% of the simulations in the PSA. The full incremental results are summarised in Table 13.

Table 13 Diagnosis of latent TB in children: base-case cost–utility results

Strategy	Mean[a]		Incremental[b]			Probability most cost effective[c]
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
TST(≥ 10 mm)	300.21	23.088	N/A	N/A	N/A	0.032
T-SPOT.TB	332.46	23.091	32.25	0.003	Extendedly dominated	0.122
TST (≥ 5 mm) +ve followed by QFT-GIT	366.45	23.092	33.99	0.001	Dominated	0.045
QFT-GIT	361.03	23.095	-5.42	0.002	8,249 (versus TST(≥ 10 mm)	0.210
TST (≥ 5 mm)	371.14	23.096	10.09	0.001	11,255 (versus QFT-GIT)	0.269
TST (≥ 5 mm) -ve followed by QFT-GIT	393.03	23.097	21.89	0.001	18,871	0.322

[a] *Results are for the initial simulated population, and any secondary TB cases generated. These values are based on the mean of the PSA simulations, to take into account parameter uncertainty.*
[b] *Compared with next-cheapest non-domimated option*
[c] *Based on a willingness to pay of £20,000/QALY; results derived from PSA simulations.*

For the immunocompromised population QFT-GIT negative followed by TST (≥ 5 mm) was the most effective strategy with an ICER of approximately £18,746 compared with T-SPOT.TB, and is the most cost-effective strategy in 40% of the simulations at a QALY threshold of £20,000. The full results are summarised in Table 14.

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Table 14 Diagnosis of latent TB in immunocompromised people: base-case cost–utility results

Strategy	Mean[a]		Incremental[b]			Probability most cost effective[c]
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
TST (≥ 10 mm)	269.42	15.516	N/A	N/A	Dominated	0.046
QFT-GIT +ve TST (≥ 5 mm)	289.31	15.516	19.89	0.000	Dominated	0.052
TST (≥ 5 mm)	276.01	15.517	-13.30	0.001	Dominated	0.067
QFT-GIT	258.61	15.523	-17.40	0.006	N/A	0.187
T-SPOT.TB	280.90	15.524	12.29	0.001	10,402.63 (versus QFT-GIT)	0.249
QFT-GIT –ve TST (≥ 5 mm)	318.26	15.526	37.36	0.002	18,746.01 (versus T-SPOT.TB)	0.399

[a] *Results are for the initial simulated population, and any secondary TB cases generated. These values are based on the mean of the PSA simulations, to take into account parameter uncertainty.*
[b] *Compared with next-cheapest non-domimated option*
[c] *Based on a willingness to pay of £20,000/QALY; results derived from PSA simulations.*

In recently arrived migrants from high-prevalence countries, TST (≥ 5 mm) dominated the TST (≥ 5 mm) positive followed by QFT-GIT, T-SPOT.TB and QFT-GIT alone strategies and had a probability of 47% of being the optimal option if QALYs are valued at £20,000. The TST (≥ 5 mm) negative followed by QFT-GIT strategy generated most QALYs, but the marginal benefit over TST (≥ 5 mm) alone was associated with an ICER of £58,720 per QALY. The full incremental analysis is summarised in Table 15.

Table 15 Diagnosis of latent TB in recently arrived migrants from high-prevalence countries: base-case cost–utility results

Strategy	Mean[a]		Incremental[b]			Probability most cost effective[c]
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
TST (≥ 5 mm) +ve QFT-GIT	300.10	19.909	N/A	N/A	Dominated	0.032
T-SPOT.TB	400.12	19.915	100.02	0.006	Dominated	0.042
QFT-GIT	291.13	19.917	-108.99	0.002	N/A	0.177
TST (≥ 5 mm)	298.75	19.922	7.62	0.005	1,524	0.469
TST (≥ 5 mm) -ve QFT-GIT	353.47	19.923	54.72	0.001	58,720	0.280

[a] *Results are for the initial simulated population, and any secondary TB cases generated. These values are based on the mean of the PSA simulations, to take into account parameter uncertainty.*
[b] *Compared with next-cheapest non-domimated option*
[c] *Based on a willingness to pay of £20,000/QALY; results derived from PSA simulations.*

The authors note that the results of the health economic analysis should be taken in context of the limitations of the clinical review. In particular, it is acknowledged that the BCG

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vaccination history may have an impact on the diagnostic accuracy (and subsequent cost effectiveness) of the tests considered.5 mm

A full copy of Warwick Evidence's report is provided as appendix H.

3.1.3.44 Evidence statements [2015]

Children

Moderate to high quality evidence from the three prospective studies suggested no significant difference between QFT-GIT and TST-5 mm (pooled R-CIR = 1.12, 95% CI: 0.72, 1.75). QFT-GIT performed significantly better than TST-10 mm in identifying latent tuberculosis infection or predicting risk of active tuberculosis (pooled R-CIR = 4.33, 95% CI: 1.32, 14.23).

Low to high quality evidence from five prospective studies investigating the incidence of active tuberculosis, found that there was a wide variability in sensitivity and specificity of IGRA (QFT-GIT/G) and TST (5 mm or 10 mm). Due to high unexplained heterogeneity (not explained by IGRA type and TST threshold, similar diagnostic methods of active tuberculosis), no meta-analysis could be performed. IGRA (QFT-GIT/G) demonstrated similar sensitivity (range: 48%-100%) and slightly better specificity (range: 49%-90%) compared to TST 5 mm (sensitivity range: 57%-100%; specificity range: 45%-65%). Although, sensitivities of IGRA and TST 5 mm were higher than that for TST 10 mm/15 mm (range: 30%-56%), the corresponding specificities of these tests were lower compared to TST 10 mm/15 mm (63%-93%).

Low to high quality evidence from a meta-analysis of 14 studies showed a significantly stronger association for IGRAs compared to TST in relation to a risk of latent tuberculosis infection/exposure level (pooled R-DOR = 1.98, 95% CI: 1.19, 3.28; I2 = 89%). The subgroup analysis by country of burden explained some (but not all) of the observed heterogeneity and revealed a trend showing no difference between IGRAs and TST in identifying LTBI across studies conducted in countries of high TB burden (pooled R-DOR = 1.13, 95% CI: 0.78, 1.65; I2 = 71). In contrast, IGRA was significantly superior to TST in identifying latent tuberculosis infection in the settings of low tuberculosis burden (pooled R-DOR = 4.74, 95% CI: 2.15, 10.44; I2 = 67%). In 5 studies both tests revealed strong associations of increasing order across exposure gradient for most exposures (sleeping proximity, adult index case type of tuberculosis diagnosis, adult index case smear grade, tuberculosis contact score, and relationship to index case).

Low to high quality evidence from 7 studies found mixed findings on whether or not the BCG vaccination status influenced the odds of test positivity differentially for IGRAs and TST. Out of seven studies reporting relevant data, only three demonstrated significantly increased ORs for TST positivity in relation to BCG vaccination status (range of ORs: 1.16-20.34). The odds of test positivity for IGRAs across the 6 studies were not significantly different between the BCG vaccinated vs. non-vaccinated groups. One large study showed there was a statistically significant association between BCG vaccination status and an increased odds of test positivity for TST (OR = 1.16, 95% CI: 1.0, 1.33) but not for IGRA (OR = 0.99, 95% CI: 0.86, 1.12).

Low to high quality evidence from 17 studies found a wide variation in kappa statistic, ranging from 0.13 to 0.91. In post-2009 studies, the ranges of kappa statistic according to specific TST threshold and IGRA type were as follows: QFT-GIT vs. TST 5 mm (range: 0.27-0.91), QFT-GIT vs. TST 10 mm (range: 0.13-0.64), and TSPOT vs. TST 10 mm (range: 0.53-0.71).

A directly applicable health economic analysis with minor limitations suggests there is considerable uncertainty around the cost-effectiveness of different diagnostic tests for case-finding of LTBI in children, with a 2-step testing approach using TST (≥ 5 mm) negative

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followed by QFT-GIT having a 32% probability of being cost-effective at a QALY value of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status.

Immunocompromised people

Moderate to high quality evidence from 2 studies found that the reported R-CIRs comparing IGRAs (QFT-G/GIT or T-SPOT.TB) with TST were not statistically significant (with 95% CIs), rendering these results as inconclusive. Moderate quality evidence from one study showed that QFT-GIT performed better than TST (at 5 mm or 10 mm threshold) in identifying people with latent tuberculosis infection (incidence of active tuberculosis in QFT-GIT positives vs. TST positives: 11.54% vs. 0.0%).

Low to moderate quality evidence from 32 studies found that there was a wide variability, and an absence of a clear pattern in the estimates of sensitivity and specificity. In general, for both IGRA and TST, specificity tended to be greater than sensitivity. Some or all of the observed variation was due to zero count events (unstable estimates), underlying differences in study populations/conditions, settings, variation in exposure definitions and measurement, and TST thresholds. The heterogeneity persisted even after stratifying the estimates by the type of IGRA (QFT-GIT, TSPOT) and TST threshold (5 mm, 10 mm). In light of the observed heterogeneity, no meta-analysis was undertaken.

Low to moderate quality evidence from 26 studies found that the association between the screening test results and the risk of latent tuberculosis infection/exposure level measured with ratio of diagnostic odds ratios (R-DOR; IGRA vs. TST) in individual studies ranged from 0.07 to 8.45. The forest plot analysis of R-DORs included 21 studies and revealed significant heterogeneity across all subgroups of participants except for haemodialysis in whom IGRA (QFT-GIT) was more strongly associated with exposure groups than TST 10 mm (Pooled R-DOR = 2.53, 95% CI: 1.48, 4.34). Similarly, in participants with hepatitis C, IGRA (TSPOT) outperformed TST 5 mm in detecting latent tuberculosis infection (R-DOR = 8.45, 95% CI: 3.71, 19.24). For most subgroups the within-subgroup heterogeneity by IGRA type (QFT-GIT, TSPOT) and TST threshold (5 mm, 10 mm, 15 mm) could not be examined due to sparse data. In people with HIV/AIDS, TST 10 mm performed significantly better than QFT-GIT (Pooled R-DOR = 0.35, 95% CI: 0.15, 0.83). For the remaining subgroups (e.g., lupus erythematosus, solid organ transplantation candidates, kidney transplant recipients), the performance of QFT-GIT did not significantly differ from that of TST (wide 95% CIs and inconclusive results).

Low to moderate quality evidence indicated no differential effect of BCG vaccination status on IGRA and TST positivity in the 14 newly identified studies reporting the association between test positivity and BCG vaccination status. Only one study demonstrated significantly increased OR for TST-10 mm positivity (OR = 4.28, 95% CI: 1.35, 13.64) as opposed to the non-significant OR for IGRA (OR = 1.89, 95% CI: 0.75, 4.73) in relation to BCG vaccination status.

Low to high quality evidence found that percent concordance and kappa ranges between QFT-GIT and TST according to each condition were as follows: HIV (concordance: 75%-96%; kappa: 0.29-0.48), hematologic disorders (concordance: 70.6%-80%; kappa: 0.09-0.16), solid organ transplantation candidates (concordance: 65%-80%; kappa: 0.19-0.57), post kidney transplantation (concordance: 80%; kappa: 0.09-0.27), end-stage renal disease/haemodialysis (concordance: 60%-86.4%; kappa: 0.21-0.49), and immune-mediated inflammatory diseases before anti-TNF-α therapy (concordance: 60%-93%; kappa: 0.08-0.56). Three studies reported between-test agreement parameters by BCG vaccination status, which showed lower percent concordance and kappa values for BCG vaccinated vs. non-vaccinated participants.

A directly applicable health economic analysis with minor limitations suggests there is some uncertainty around the cost-effectiveness of different diagnostic tests for identifying LTBI in

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immunocompromised people, with a two-step testing approach using QFT-GIT followed by TST (≥ 5 mm) for people with negative IGRAs having a 40% probability of being cost-effective at a QALY value of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status.

Recent arrivals from countries with a high incidence of TB

Low to high quality evidence from 2 studies which correlated IGRA (QFT-GIT and TSPOT) and TST results with cumulative incidence of active tuberculosis showed no significant difference in CIRs for QFT-GIT vs. TST-5 mm (R-CIR = 2.55, 95% CI: 0.57, 11.40) and QFT-GIT vs. TST-10 mm (R-CIR = 0.87, 95% CI: 0.17, 4.56). The pooled estimate of R-CIRs across the two studies was not significant (pooled R-CIR = 1.57, 95% CI: 0.52, 4.76). Based on two studies, QFT-GIT demonstrated greater specificity values (range: 46%-71%) compared to TST (range: 15%-49%), but lower sensitivity (pooled estimate: 76%) compared to TST (pooled estimate: 94%). One study showed TST-15 mm to have performed better than TSPOT both in terms of sensitivity (87% vs. 75%) and specificity (44% vs. 40%).

Low quality evidence from a meta-analysis of 3 studies found that the pooled R-DOR for IGRA (QFT-GIT) vs. TST-10 mm (contact with TB case, exposure to TB, birth in TB burden country) was not statistically significant, suggesting no evidence of IGRA performing better than TST in identifying latent tuberculosis infection. Seven of the 10 studies reviewed in CG117 found significant strong associations presented as DORs for both IGRA and TST (5 mm, 10 mm, 15 mm) across exposure gradient groups defined as place of birth, racial group, country prevalence. However, the R-DORs comparing IGRA to TST across these studies ranged from 0.14 to 0.98. Since the CG117 report did not provide the 95% confidence intervals, it is not clear what the predictive performance of IGRA relative to TST was in terms of identifying LTBI.

Low quality evidence from 1 study found that there was no evidence indicating a differential effect of BCG vaccination status on IGRA (QFT, TSPOT) and TST positivity. The odds of test positivity for QFT-GIT (OR = 1.70, 95% CI: 0.80, 3.60), TSPOT (OR = 1.80, 95% CI: 0.80, 4.00), and TST (OR = 1.70, 95% CI: 0.80, 3.50) were not significantly different between the BCG vaccinated vs. non-vaccinated groups.

Low quality evidence from 12 studies, overall percent concordance between IGRA and TST-10 mm ranged from 63.6% to 84.2%. The corresponding concordance between IGRA and TST-5 mm was similar (range: 60.7%-90%). Most kappa values between IGRA and TST (regardless of TST threshold and BCG vaccination status) were below the value of 0.45. Both concordance and kappa were greater amongst BCG unvaccinated.

A directly applicable health economic analysis with minor limitations suggests there is some uncertainty around the cost-effectiveness of different diagnostic tests for the opportunistic screening of LTBI in newly arrived people from high-incidence countries, with a single TST (≥ 5 mm) having a 47% probability of being cost effective at a QALY value of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status.

3.1.3.5 Evidence to recommendations [2015]

Relative value of different outcomes	The GDG agreed that it was important to evaluate the best approach to diagnosing latent TB infection in the population subgroups outlined here, namely children, people who are immunocompromised or at risk from immunosuppression, and recent arrivals from countries with a high incidence of tuberculosis. Currently, there is no diagnostic gold standard for identification of individuals with latent tuberculosis infection. Instead, the available screening tests for latent infection provide indirect assessment of

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	the presence of infection by relying on a host's immunological response to tuberculosis antigens. In addition, none of the available tests can accurately differentiate between people with latent tuberculosis infection and active tuberculosis. The GDG emphasised that the question here is about providing guidance in situations where a decision to offer a test has already been made and evidence-based recommendations on what tests to perform are needed.
Trade off between clincial benefits and harms	Detecting latent tuberculosis infection in these subgroups may be beneficial because of their increased relative risk of progression to active, potentially infectious tuberculosis compared to the general population. Treating latent infection before it progresses to active disease therefore can prevent onward transmission and the associated harms and costs of active tuberculosis. However, the treatment of latent tuberculosis involves the use of hepatotoxic drugs – such as isoniazid and rifampicin – which means that the individual patient's risk of progression to active disease must be weighed up against the possibility of potentially serious treatment side effects. This also means that a trade-off is evident in the choice of diagnostic strategy as there are negative consequences associated with false negative (untreated latent infection and possible progression) and false positive (unnecessary exposure to potentially toxic drugs) test results. In neonates (children aged less than 4 weeks) who have been in close contact with people with pulmonary TB, the group felt that it was appropriate to recommend that clinicians first assess the child for active TB and initiate 3 months of treatment for latent TB with isoniazid before initiating diagnostic efforts for latent TB. This is because the immune system in a neonate has not yet developed and, therefore, exposure to TB means a significantly increased risk that the child has been infected. Early treatment is particularly vital because the underdeveloped immune system in a neonate means they are at an increased risk of progression to active disease, but also of progressing to more severe forms of the disease such as disseminated disease or disease with central nervous system involvement. The lack of immune system in neonates also means that there can be a higher proportion of false negatives as the tests rely upon the body's immune response. Furthermore, it is unlikely – whether infected in utero or after birth – that a neonate has experienced a sufficient period of incubation to be detected by Mantoux or IGRA testing. In young children aged between 4 weeks and 2 years who have been in close contact with people with pulmonary TB, the group recommended that treatment for latent infection (3 months of isoniazid) be initiated and a Mantoux test concurrently performed. The underdeveloped immune system of these young children means that they are still at an elevated risk of infection from contacts, as well as for progression to active disease. For the reasons outlined above for neonates, the group felt that early initiation of treatment for latent infection is vital in avoiding disease in these contacts. However, the immune system has begun to develop in these children and has now reached a level that enables the use of tests for latent TB. Over the age of 2 years, the group felt that diagnosis of latent TB and the actions associated with it should be as for adults. This is because the immune system has now sufficiently developed to reduce the risk of both infection and progression to active disease, as well as to provide a sufficient immune response to allow the tests to function. The GDG noted that Mantoux testing can interfere with the results of IGRA testing, and therefore result in false-positive diagnosis. Therefore, in the case of two-step testing, the tests should be performed relatively close together. In young children, the immune system takes longer to develop, so the diagnostic window may need to be longer to accommodate this to attempt to minimise false-negatives. However, there is a trade-off between waiting for a more reliable test, and the decreasing effectiveness of

	treatment for latent tuberculosis due to the much faster progression rates in children.
Trade-off between net health benefits and resource use	The GDG reviewed health economic modelling undertaken by Warwick Evidence addressing the 3 subpopulations of interest for this update. It noted that all 3 analyses suggested that the tests with highest sensitivity provide best value for money. This is because, in the situations modelled, the harms and costs of false-negative diagnoses (imperfect sensitivity) tend to outweigh the harms and costs of false-positive diagnoses (imperfect specificity). This meant that, where TSTs are used, a 5 mm threshold provides a better balance of benefits and harms than a 10 mm cut-off because, for any 2 thresholds, the lower one will automatically have better sensitivity whereas the higher one will always have better specificity. The model for **children** suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for **recent arrivals from countries with a high incidence of TB** also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for **immunocompromised people** relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone). The GDG considered the substantial resource implications inherent in the potential widespread use of IGRA testing, particularly in children who would require multiple appointments and blood taken in a children's hospital (thereby raising costs). In addition, for those strategies that would involve increasing the amount of TST testing, there is a need to consider that the reagent used in Mantoux tests is currently rationed to services as there is a global shortage. The GDG emphasised the importance of clarity regarding the application of these recommendations to case finding in high risk groups as opposed to blanket screening. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. The magnitude of the impact BCG status has on the diagnostic accuracies and cost effectiveness of the tests examined could not be established quantitatively due to poor reporting of BCG vaccination in the evidence. However, the group noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses. It could be inferred that the overall impact of BCG status on the accuracy of these results for decision making purposes is likely to be small. For these reasons, the GDG chose not to recommend that a different TST threshold (or a different test) should be adopted in people with a history of BCG, as some other guidelines

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	(including previous versions of NICE guidance) do.
Quality of evidence	Since previous NICE guidance has specified a 6 mm threshold for TST-positivity, the GDG was keen to explore the impact of different thresholds (5 mm vs 6 mm). However, only 2 studies considered a 6 mm induration threshold (but were excluded from the health economic evaluation) and did not describe a head-to-head comparison of 5 mm and 6 mm thresholds. It was not possible, therefore, to evaluate the numbers of patients who would be classified as having latent tuberculosis given a 6 mm compared with a 5 mm threshold for test positivity. It was noted that all evidence on which previous guidance was based also used a 5 mm, not a 6 mm, threshold. Currently, the Green Book[g] recommends a 6 mm threshold, but the GDG noted that it was unclear what evidence this was based on and that the Green Book is principally concerned with vaccination rather than diagnosis. Given the lack of substantive evidence on which to recommend a 6 mm induration cutoff , the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold. There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the group noted that reliably measuring the difference between 5 mm and 6 mm in practice was extremely difficult. The GDG was also keen to explore the impact that BCG status on test results. However, diagnostic accuracy results were not stratified by BCG status in the literature identified, so this could not be explored directly. However, the GDG understood that a significant proportion of participants in the studies had undergone a BCG (on average across the evidence base, 92% of children, 47% of immunocompromised and 38% of newly arrived immigrants). The GDG thought it was particularly significant that a TST induration threshold of 5 mm was estimated to be the most cost effective to adopt in children, even though a substantial majority of them had a history of BCG (in other words, it could be seen that any increase in false-positive diagnoses did not outweigh the benefit of maximising sensitivity). Therefore, the GDG concluded that the results of the health economic model could be assumed to apply to people at risk of latent TB regardless of BCG status, and chose not to make separate recommendations for people with a history of BCG in any of the populations of interest. The studies identified in this review are highly heterogeneous in terms of tests used, as well as the threshold for test positivity investigated, setting, and risk of latent infection in the populations under consideration. Additionally, the incidence studies included in the clinical evidence varied in terms of length of follow-up. Evidence on certain subgroups – including people coinfected with HIV – was scarce, with the GDG noting that these groups would represent a large proportion of the patients who would be considered at high risk for latent tuberculosis infection. Overall, while the number of studies identified was substantial, the variation in participants investigated and subgrouping of the studies of immunocompromised patients mean that the evidence is limited for each subgroup of patients considered. Additionally, the GDG noted that the immunocompromised patients in the included studies were quite significantly immunocompromised, and therefore this evidence may not capture the full spectrum of patients who would be classed as such. The GDG noted that exposure was generally ill-defined lacking a description of duration and proximity of contact to TB cases. Risk of latent tuberculosis infection was frequently presented using proxy measures, including birth or residence in a high TB incidence country, profession, abnormal chest x-ray and drug abuse. There were some gaps in the

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[g] Public Health England (2014) Immunisation against infectious disease: the Green Book. Public Health England: London

	reporting of information on study setting, age, gender and level of BCG vaccination of the study population. BCG vaccination status will impact the results of tests for latent tuberculosis, but the studies presented seldom reported the necessary granularity to quantify the impact of BCG status on diagnostic accuracy in these populations. The level of heterogeneity in the clinical evidence precluded any pooled analysis of the results, although the group noted that despite this the evidence was utilised in the health-economic analysis. The GDG agreed that this was acceptable given the probabilistic nature of the health economic modelling, which incorporated the full range of uncertainty present in parameters derived from the clinical evidence and therefore reflects this uncertainty in the output of the model. Risk of bias and the quality of the studies were assessed separately for incidence and exposure group respectively. Out of 45 included studies, risk of bias was assessed in 11 studies relating to incidence group and quality of the studies were assessed in the remaining 34 studies related to exposure to TB group. Out of the 11 studies (incidence group studies), five studies were identified as having high risk of bias, four as medium risk of bias and the remaining two was rated as being low risk of bias. All had important drawbacks in design, methods and key outcomes coverage; with unlimited and unclear information leading to possible bias in the studies. Of the 34 studies (exposure group studies), the majority of the studies (n = 28) were generally of lower quality, five were rated as moderate quality and one study was of high quality.
Other considerations	The GDG noted that the relative costs, benefits and harms of case-finding were shown to be sensitive to the level of tuberculosis incidence, with cost-effectiveness increasing in high incidence settings. The GDG noted that the background incidence of multidrug resistant tuberculosis might influence the decision to opportunistically screen and treat a patient given a positive test result, particularly with regards case-finding amongst newly arrived patients. The GDG agreed that the relative benefits and harms of case-finding, and any subsequent treatment, should be discussed with the patient when offering the test. Whilst the tests explored here cannot distinguish between latent and active tuberculosis, the GDG pointed out that the key differentiating factor in young children and neonates is the presence or absence of weight gain. The GDG emphasised the results of the economic analysis suggest that cost-effectiveness increases with prevalence and activation rates, and therefore case-finding should be encouraged for patients with elevated risk of tuberculosis. In addition, the GDG felt it would be useful therefore to have a general framework for a consensus-based risk model that would help identify these patients and would recommend research in this area.

3.1.42 Recommendations and research recommendations

3 Adults

4 1. Offer Mantoux testing to diagnose latent TB in adults aged 18 to 65[h] who are:

5 • household contacts of a person with pulmonary TB[i]

[h] The upper age limit for offering testing to diagnose latent TB was previously 35 years, but has been increased to 65 years. Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years. Therefore, it is necessary to update this recommendation to reflect the revised upper age-limit for treatment.

[i] The Committee has revised this recommendation – which previously referred to 'all people with active TB' – to limit testing to contacts of people with potentially infectious TB.

- non-household contacts (other close contacts for example, in workplaces) of people with pulmonary TB[j].

  An induration of 5 mm or larger, regardless of BCG history, is considered a positive test result[k]. **[2011, amended 2015]**

2. **Consider interferon-gamma testing for adults aged 18 to 65[l] whose Mantoux test shows positive results (5 mm or larger, regardless of BCG history)[m], or in people for whom Mantoux testing may be less reliable, for example, BCG-vaccinated people. [2011, amended 2015]**

3. **If Mantoux test is inconclusive, refer the person to a TB specialist. [2011]**

Children and young people

4. **Only consider using interferon-gamma release assays in children and young people if Mantoux testing is not available or is impractical (for example, situations in which large numbers need to be tested). [new 2015]**

5. **If a neonate has been in close contact with people with pulmonary TB and has not had at least 2 weeks of anti-TB treatment:**
   - Assess for active TB.
   - Start isoniazid for 3 months.
   - Carry out a Mantoux test after 3 months of treatment.
   - If the Mantoux test is positive (5 mm or larger, regardless of BCG history), reassess for active TB (see section 1.3.1). If this assessment for active TB is negative, continue isoniazid for a total of 6 months.
   - If the Mantoux test is negative, consider an interferon-gamma release assay:
     - if both are negative then stop isoniazid and give a BCG vaccination
     - if the interferon-gamma release assay is positive, reassess for active TB; if the test for active TB is negative, continue isoniazid treatment for a total of 6 months. **[new 2015]**

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[j] The Committee has revised this recommendation – which previously referred to 'all people with active TB' – to limit testing to contacts of people with potentially infectious TB.

[k] Although not updated by a new review, the Committee felt strongly that the threshold for test positivity in adults should be brought in line with both international guidance and the other recommendations in this section. The threshold for test positivity of 6 mm in the previous NICE guideline (which was taken from the Department of Health's Green Book) is inconsistent with the new recommendations, which opted for a threshold of 5 mm, as well as with the new clinical- and cost-effectiveness reviews and the new health economic modelling on which these were based. This is particularly an issue given that the previous NICE guideline recommendations were consensus-based, not driven by evidence. See section 4.1.3.4 for further information.

[l] The upper age limit for offering testing to diagnose latent TB was previously 35 years, but has been increased to 65 years. Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years. Therefore, it is necessary to update this recommendation to reflect the revised upper age-limit for treatment.

[m] Although not updated by a new review, the Committee felt strongly that the threshold for test positivity in adults should be brought in line with both international guidance and the other recommendations in this section. The threshold for test positivity of 6 mm in the previous NICE guideline (which was taken from the Department of Health's Green Book) is inconsistent with the new recommendations, which opted for a threshold of 5 mm, as well as with the new clinical- and cost-effectiveness reviews and the new health economic modelling on which these were based. This is particularly an issue given that the previous NICE guideline recommendations were consensus-based, not driven by evidence. See section 4.1.3.4 for further information.

6. **Treat children aged between 4 weeks and 2 years and in close contact with people with pulmonary TB as follows:**
   - Start isoniazid and carry out a Mantoux test.
   - If the Mantoux test is positive (5 mm or larger, regardless of BCG history), assess for active TB.
   - If active TB is ruled out, give full treatment for latent TB infection.
   - If the Mantoux test is negative, continue isoniazid for 6 weeks, then repeat the Mantoux test and consider an interferon-gamma release assay:
     - if the repeat tests are negative, isoniazid may be stopped; give a BCG vaccination if the child has not already had one
     - if either repeat test is positive, assess for active TB and if the assessment is negative, complete treatment for latent TB. **[new 2015]**

7. **Refer children younger than 2 years and in close contact with people with smear-negative pulmonary TB to a specialist to determine what testing strategy for latent TB would be most appropriate. [new 2015]**

8. **Offer Mantoux testing for latent TB in people aged between 2 and 17 years who are:**
   - household contacts of a person with pulmonary TB
   - non-household contacts (other close contacts, for example, in workplaces and schools) of people with pulmonary TB. **[new 2015]**

9. **If the Mantoux test is positive (5 mm or larger, regardless of BCG history) in people aged between 2 and 17 years:**
   - assess for active TB, and
   - consider treating them for latent TB infection. **[new 2015]**

10. **If the initial Mantoux test is negative but the child is a contact of a person with sputum-smear-positive disease, offer an interferon-gamma test after 6 weeks and repeat the Mantoux test to increase the sensitivity (to reduce false negative results). [new 2015]**

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New entrants from high-incidence countries

11. **Assess and manage TB in new entrants from high incidence countries as follows:**
    - assess risk of HIV, including HIV prevalence rates in the country of origin, and take this into account in deciding whether to give a BCG vaccination
    - offer testing for latent TB
    - assess for active TB if the test for latent TB is positive
    - offer treatment to people aged 65 years or younger in whom active TB has been excluded but who have a positive Mantoux test inconsistent with their BCG history and a positive interferon-gamma release assay for latent TB infection
    - consider offering BCG for unvaccinated people who are Mantoux negative
    - give 'inform and advise' information to people who do not have active TB and are not being offered BCG or treatment for latent TB infection. **[2006, amended 2011 and 2015]**

12. **Primary care services should support local, community-based and voluntary organisations that work with vulnerable migrants to ensure they:**

- register with a primary care provider
- know how to use NHS services (emergency or primary care). **[2012]**

13. Healthcare professionals, including primary care staff, responsible for screening new entrants should screen all vulnerable migrants who have not previously been checked (see section 1.2.1). This is regardless of when they arrived in England. People born in countries with an incidence of more than 150 per 100,000 per year should be made a priority for latent TB screening when they arrive here. [2012]

14. Offer Mantoux testing as the initial diagnostic test for latent TB infection in people who have recently arrived from a high-incidence country. If the Mantoux test is positive (5 mm or larger, regardless of BCG history):

- assess for active TB, and
- consider treating them for latent TB infection.

If this is unavailable offer an interferon-gamma release assay test. **[new 2015]**

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People who are immunocompromised

15. If latent TB is suspected in children and young people who are immunocompromised, refer to a TB specialist. [2015]

16. In adults who are anticipated to be or are currently immunocompromised, do a risk assessment to establish whether testing should be offered, taking into account their:

- risk of progression to active TB based on how severely they are immunocompromised and for how long they have been immunocompromised
- risk factors for TB infection, such as country of birth or recent contact with an index case with suspected infectious or confirmed pulmonary or laryngeal TB. **[new 2015]**

17. For adults who are severely immunocompromised, such as those with HIV and CD4 counts of fewer than 200 cells/mm^3, or after solid organ or allogeneic stem cell transplant, offer an interferon-gamma release assay and a concurrent Mantoux test. If either test is positive (for Mantoux, this is an induration of 5 mm or larger, regardless of BCG history):

- assess for active TB, and
- consider treating them for latent TB infection. **[new 2015]**

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18. For other adults who are immunocompromised, consider an interferon-gamma release assay alone or an interferon-gamma release assay with a concurrent Mantoux test. If either test is positive (for Mantoux, this is an induration of 5 mm or larger, regardless of BCG history):

- assess for active TB, and
- consider treating them for latent TB infection. **[new 2015]**

Contacts – outbreak situation

19. In an outbreak situation when large numbers of people may need to be screened, consider a single interferon-gamma release assay for people aged 18–65 years[n]. [2011, amended 2015]

[n] The upper age limit for offering testing to diagnose latent TB was previously 35 years, but has been increased to 65 years. Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of

Healthcare workers

20. Offer a Mantoux test to new NHS employees who will be in contact with patients or clinical materials, if the employees:

- are not new entrants from high-incidence countries and
- have not had BCG vaccination (for example, they are without a BCG scar, other documentation or a reliable history). [2011]

21. Offer Mantoux testing as the initial diagnostic test for latent TB infection in new NHS employees who have recently arrived from a high-incidence country. If the Mantoux test is positive (5 mm or larger, regardless of BCG history):

- assess for active TB, and
- consider treating them for latent TB infection.

If this is unavailable offer an interferon-gamma release assay test. [new 2015]

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22. Offer an interferon-gamma release assay test to new NHS employees who have had contact with patients in settings where TB is highly prevalent. [2011, amended 2015]

23. Healthcare workers who are immunocompromised should be screened in the same way as other people who are immunocompromised. [2011]

Under-served groups

24. Offer adults aged 18–65 years from under-served groups a single interferon-gamma release assay. [2011, amended 2015]

25. Substance misuse services with access to an interferon-gamma release assay should provide testing for adults aged 18–65 years[o] if they:

- live in a high incidence area
- are likely to be involved with substance misuse services or other support services on a regular basis (for example, for opioid substitution therapy), when support should be available for directly observed preventive therapy. [2012, amended 2015]

26. In high incidence areas (and at prisons that receive prisoners from high incidence areas), prison health services should offer an interferon-gamma release assay test

treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years. Therefore, it is necessary to update this recommendation to reflect the revised upper age-limit for treatment..

[o] The upper age limit for offering testing to diagnose latent TB was previously 35 years, but has been increased to 65 years. Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years. Therefore, it is necessary to update this recommendation to reflect the revised upper age-limit for treatment.

Upd

for TB to inmates younger than 65 years[p] who are in regular contact with substance misuse services or other support services. This is provided arrangements have been made for this support to continue after release. [2012, amended 2015]

27. **Substance misuse services and prison health services should incorporate interferon-gamma release assay testing with screening for hepatitis B and C, and HIV testing. They should refer prisoners and people who misuse substances with positive interferon-gamma release assay tests to local multidisciplinary TB teams for further clinical investigations. For prisoners, these investigations should be done in the prison if practically possible. [2012, amended 2015]**

Research recommendations

1. **Which strategies and interventions are effective and cost effective in promoting the uptake of diagnostic efforts for people with suspected latent TB, and in promoting the uptake of and adherence to treatment in those with a positive diagnosis?**

Why this is important

Identifying and effectively treating people with latent TB is a cornerstone of TB control. Encouraging people at risk of infection to be tested and have treatment is therefore vital. Despite this, the Committee found little evidence on strategies to promote these. Randomised controlled trials in at-risk populations are needed.

3.2 Diagnosing active pulmonary tuberculosis: clinical signs, symptoms or risk factors [2011]

Post-primary tuberculosis may be asymptomatic in the early stages, but symptoms, which can be either constitutional or respiratory, soon develop. Malaise, weight loss, fever and night sweats are the common constitutional symptoms. Cough is the commonest pulmonary symptom, which is initially dry and non-productive but may later become productive, with haemoptysis in a small minority of cases. Breathlessness is a late feature, usually only occurring when a substantial amount of lung is destroyed or there is a significant pleural effusion. Chest pain is relatively uncommon, but can be pleuritic if peripheral lesions are present, or of dull ill-localised nature.

A study in Sudan, grading sputum smear positivity with clinical features showed multiple chest symptoms were positively correlated with sputum smear positivity. Also, the longer the duration of symptoms, the more this correlated with sputum smear positivity. A comparison of the 'classic' symptoms of tuberculosis in patients with and without tuberculosis is summarised in Table 16.

[p] The upper age limit for offering testing to diagnose latent TB was previously 35 years, but has been increased to 65 years. Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years. Therefore, it is necessary to update this recommendation to reflect the revised upper age-limit for treatment.

Table 16: Classic symptoms of tuberculosis

Symptom	TB (n=47)	Non-TB (n=516)	Odds ratio (95% CI)
Cough	81%	77%	1.27 (0.58–2.69)
Fever	70	59	1.64 (0.85–3.15)
Weight loss	64	27	4.74 (2.53–8.86)q
Night sweats	55	27	3.29 (1/79–6.04)q
Dyspnoea	47	50	0.88 (0.48–1.60)
Chest pain	27	26	1.08 (0.55–2.11)

A multivariate analysis showed that the following features were positively associated with culture proven tuberculosis:

- the presence of TB risk factors or symptoms (OR 7.9)
- a positive skin test for tuberculosis (OR 13.2)
- a high temperature (OR 2.8)
- upper lobe disease on a chest radiograph (OR 14.6).

and that the following were negatively correlated with tuberculosis:

- shortness of breath (OR 0.2)
- crackles on physical examination of chest (OR 0.29).

3.31 Diagnosing active pulmonary tuberculosis: tests

3.3.12 Clinical introduction

Culture has been, and still is, the gold standard for diagnosing active pulmonary TB disease. Traditionally, mycobacteria have been grown on solid media, containing a mix of antimicrobial agents that allow only mycobacteria to replicate. Commonly used media include the egg-based Löwenstein-Jensen and Ogawa media, and the agar-based Middlebrook 7H9, 7H10 and 7H11. *M. tuberculosis* growth is distinct, producing either beige-coloured, rough, dry, corded, flat colonies with irregular borders or warty, granular colonies that over time heap into a cauliflower shape.

Although generally regarded as the most sensitive of currently available tests, with the added benefit that it also permits drug sensitivity tests to be made, culture is an imperfect gold standard. This is because it can take 2 to 8 weeks for the isolation of *M. tuberculosis* from a clinical specimen, and in 10 to 20% of cases the bacillus is not successfully cultured.

The time to detection of mycobacterium can be shortened with the use of automated or semi-automated liquid culture systems. Systems that rely on non-radiometric growth have been developed. These include the MycoBacT system and the BACTEC MGIT 960. These systems measure changes in carbon dioxide production or oxygen consumption fluorimetrically or colorimetrically, and allow continuous monitoring of cultures.

Smear microscopy is used to examine specimens for the presence of acid-fast bacilli. This, in addition to culture, constitutes part of current practice for diagnosing active pulmonary tuberculosis in people with suspected disease. Sputum smears are prepared by spreading portions of the sputum specimen on a glass slide and applying a stain. A variety of different stains are available, but the most common are the Ziehl-Neelsen, auramine-rhodamine fluorochrome and Kinyoun stains. Fluorescent staining is considered to be more sensitive. Microscopy indicates that acid-fast bacilli are present in the sample, but does not always indicate viable or living organisms *per se* or that the organism is *M. tuberculosis*.

[q] significant difference

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A chest x-ray is also part of the standard battery of tests used in the diagnosis of people with suspected pulmonary disease. A posterior-anterior x-ray is the standard view used. In active disease, infiltrates or consolidations and/or cavities are often seen in the upper lungs, with or without mediastinal or hilar lymphadenopathy. However, lesions may appear anywhere in the lungs, and in some people, such as those with HIV or who are immunosuppressed, the chest x-ray may even appear normal.

Nucleic acid amplification tests (NAATs) are molecular systems which are able to detect small amounts of genetic material from the mycobacterium by repeatedly amplifying target sequences. If the target organism is not present in the sample, no amplification will occur. Polymerase chain reaction is the most common of the amplification methods; the DNA products are analysed on an agarose gel, which separates the products according to size against a molecular weight marker. Detection of the amplified products can also be performed by DNA sequencing, enzyme immunoassay using probe-based colorimetric detection or by fluorescence emission technology. The use of NAATs reduces the time for identification of M. tuberculosis to just 3 to 6 hours after the specimen is processed. Commercially available NAATs include the GeneXpert MTB/RIF test, the Amplicor Mycobacterium Tuberculosis test, the Amplified Mycobacterium Tuberculosis Direct Test, and the BDProbeTec and BDProbeTec ET tests. Data for the Ligase Chain Reaction assay was not included in this review as it is no longer available in the UK.

Phage-based tests consist of cultures infected with bacteriophages that specifically target M. tuberculosis. Exogenous, non-infecting phages are destroyed, and the signal is amplified. One type of signal is the emission of light, produced by expression of a reporter gene, the luciferase gene, inserted into the phage genome. A simpler method, which does not rely on recombinant phage, is to use the release of progeny phage (phage amplification) as the signal. These methods can also be used for drug susceptibility testing as incubating the culture with the relevant antimicrobials will mean that only viable mycobacteria will be detected.

Numerous antibody detection assays for TB have been developed over the years; these have used a variety of antigens to detect certain antibodies, including immunoglobulin G (IgG), immunoglobulin M (IgM) and lipoarabinomannan (LAM). Since exposure to atypical mycobacteria, vaccination and HIV prevalence influences results of these tests, accuracy reports of these tests vary in different settings. However, thus far none of these tests have shown adequate – and consistent – accuracy, and so have not been widely implemented or recommended.

Adenosine deaminase assays (ADAs) detect adenosine deaminase activity in serum and plasma samples. The test is based on the principle that tuberculous effusions show significantly higher levels of adenosine deaminase activity compared with effusions due to other underlying lesions.

Tuberculin skin tests (TSTs) are based on the detection of a response to purified protein derivative (PPD) in people with suspected infection or disease. PPD is a mixture of antigens shared by several mycobacteria that gives rise to a delayed-type hypersensitivity skin reaction. TSTs are relatively cheap and can be performed without the need for a specialist laboratory. They are currently a standard tool in the detection of latent TB infection (LTBI), although their use in the diagnosis of active disease is widely disputed. Difficulties in the administration and interpretation of TSTs often lead to false results for both LTBI and active disease. PPD doses that are too low increase the likelihood of false-negative results, and doses that are too high increase the likelihood of false-positive results. The technique for administering PPD may also cause false results, and thresholds for interpretation vary between countries. Additionally, because the antigens contained within the PPD are shared with other mycobacteria, tuberculin reactivity – and a resulting positive TST – may result from BCG vaccination or exposure to atypical mycobacteria.

Interferon-gamma release assays (IGRAs), like TSTs, are currently a standard tool in the detection of LTBI but, again, like TSTs, their use in the diagnosis of active disease is widely disputed. Blood samples obtained from the patient are incubated with mycobacterial antigens specific for M. tuberculosis. T lymphocytes within the blood sample produce interferon-gamma as a marker of infection or active TB; therefore, assessment of whether a patient's T cells have been exposed to and sensitised by antigens specific to M. tuberculosis, may provide an alternative approach to diagnosis.

IGRAs have several advantages over TST. They involve having a blood test at a single visit and a return visit might not be needed in some settings, depending on the test result. Automated testing has the advantage of reducing reader bias as interpretation is objective. Furthermore, they are believed to be less likely than TSTs to give false-positive results in BCG-vaccinated people and that are better able to discriminate between most atypical mycobacteria and *M. tuberculosis*.

3.3.2 Review question

Apart from culture, what other tests are effective in establishing an accurate diagnosis of active pulmonary TB in a) adults and b) children and young people with suspected pulmonary TB?

In the presence of a negative culture, what other tests may support an accurate, positive diagnosis in people with suspected pulmonary TB?

3.3.3 Evidence review

This evidence review aimed to establish which test is the most effective in establishing an accurate diagnosis of active pulmonary TB whilst the results of culture are awaited. It also considered which diagnostic method is associated with the shortest time from start of symptoms or start of diagnostic efforts to diagnosis or treatment initiation.

Studies of interest were those that assessed the effectiveness of different diagnostic tests compared to a culture-based gold standard for the diagnosis of pulmonary TB. Tests contained in the review include smear microscopy, chest x-ray, nucleic acid amplification tests (NAATs), phage-based tests, antibody detection assays, interferon gamma release assays and tuberculin skin tests.

For this review, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the diagnosis of active pulmonary tuberculosis. Test-and-treat RCTs, quasi-RCTs, cross-sectional studies and systematic reviews of these study designs were considered for inclusion. Papers of interest were those that compared diagnostic methods against a culture-based reference standard. (See appendix C for the full review protocol).

Trials were excluded if:

- participants did not have suspected TB;
- the reference standard was not culture-based;
- tests were not conducted concomitantly;
- the test used was 'in-house' rather than a commercial test;
- the sample size was less than 30, unless pooled in a meta-analysis;
- for diagnostic test accuracy data, studies in which a 2x2 table could not be populated;

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- case-control studies, case studies, case series and narrative reviews.

From a database of 4515 abstracts, 494 full-text articles were ordered (although this included possible inclusions for suspected extrapulmonary disease) and 90 papers met the inclusion criteria. This represented 81 papers containing 257 evaluations in adults, and 9 papers containing 31 evaluations in children. 1 further paper, which examined the use of a computer-aided radiograph-reading system, was identified in the course of the update searches.

Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used the 'metandi' command in STATA to meta-analyse the data into pooled effect estimates. Where STATA was not appropriate – for example, where there were fewer than 4 data points to pool – the 'mada' command in R was used, though this can only produce pooled estimates for sensitivity, not specificity. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

Subgroup analyses could be made by age, HIV status and smear positivity.

No evidence was identified for participants who were culture negative.

The quality of the data for each outcome ranged from high to very low, though most outcomes were low or very low. The evidence base suffered from the presence of significant heterogeneity, poor study design and reporting and a lack of generalisability to the UK context.

All recommendations were made using the recommendations made in the previous guideline (CG117) as a starting point.

3.3.4 Evidence statements

Adults

Very low quality evidence from 84 cross-sectional evaluations in 59984 specimens from people (predominantly adults) with suspected pulmonary TB comparing sputum smear microscopy with a culture-based reference standard showed microscopy to have a pooled sensitivity of 65.6% (95% CI 61.1 to 69.9%) and a pooled specificity of 97.9% (95% CI 97.1 to 98.5%). This included 40 evaluations of fluorescence microscopy, the preferred smear technique according to Public Health England's Standards for Microbiology Investigations[r]; very low quality evidence for this technique showed a pooled sensitivity of 69.2% (95% CI 62.7 to 75.1%) and a pooled specificity of 97.8% (95% CI 96.5 to 98.6%).

Moderate quality of evidence from 3 cross-sectional evaluations in 1094 adults with HIV and suspected pulmonary TB comparing microscopy with a culture-based reference standard showed microscopy to have a pooled sensitivity of just 40.8% (95% CI 18.6 to 67.6%), and a pooled specificity ranging from 90.4 to 100% (meta-analysis not possible).

Very low quality of evidence from 137 cross-sectional studies in 85438 specimens from people (predominantly adults) with suspected pulmonary TB comparing nucleic acid amplification tests (NAATs) with a culture-based reference standard showed NAATs to have a pooled sensitivity of 89.0% (95% CI 87.2 to 90.6%) and a pooled specificity of 98.1% (95% CI 97.6 to 98.5%).

Very low quality of evidence from 16 cross-sectional evaluations in 2990 adults with HIV and suspected pulmonary TB comparing NAATs (specifically, the Xpert MTB/RIF assay) with a culture-based reference standard showed NAATs to have a pooled sensitivity of 80.9% (95% CI 72.9 to 86.9%) and a pooled specificity of 98.8% (95% CI 97.8 to 99.4%)

[r] Public Health England (2014) UK Standards for Microbiology Investigations: B40 Investigation of Specimens for Mycobacterium species. Public Health England: London

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Very low quality of evidence from 66 cross-sectional evaluations in 5205 sputum smear-positive adults comparing NAATs with a culture-based reference standard showed NAATs to have a pooled sensitivity of 98.7% (95% CI 97.8 to 99.2%).

Very low quality of evidence from 9 cross-sectional evaluations in 2703 adults with suspected pulmonary TB comparing tests that detect antituberculosis antibodies (IgG, IgM, ES-31, ES-43 and ESAT-6) with a culture-based reference standard showed antituberculosis antibody detection tests to have a pooled sensitivity of just 68.2%, though there was considerable variability and uncertainty in the estimates (95% CI 40.9 to 86.9%). Very low quality of evidence from 2 cross-sectional evaluations in 370 adults with suspected pulmonary TB comparing tests that used antituberculosis antibodies (LAM) to detect TB in the serum with a culture-based reference standard showed the tests that used antituberculosis antibodies to have a pooled sensitivity of just 54.1%, though there was again considerable variability and uncertainty in the estimates (95% CI 30.4 to 76.2%). Data from LAM antibody tests conducted on urine samples, assessed in 3 cross-sectional evaluations, also performed poorly with regards to sensitivity (32.9% (95% CI 22.6 to 45.2%)) (very low quality evidence).

One directly applicable CUA with potentially serious limitations suggests that NAATs are not cost effective in the NHS, although this is sensitive to pre-test prevalence.

One partially applicable CUA with potentially serious limitations from a US setting found GeneXpert testing in addition to 3x sputum smear and culture, chest radiograph and DST to be cost effective at a threshold of $50,000 per QALY gained, but the underlying assumptions of cost and laboratory throughput may not transfer to the NHS.

Children and young people

Very low quality of evidence from 8 cross-sectional evaluations in 2491 children and young people (under the age of 15) with suspected pulmonary TB comparing microscopy with a culture-based reference standard showed microscopy to have a pooled sensitivity of 56.3%, though there was considerable uncertainty in the estimate (95% CI 32.7 to 77.4%), and a pooled specificity of 99.7% (95% CI 98.8 to 99.9%). This included 6 evaluations of fluorescence microscopy in 2384 children and young people; low quality evidence showed a pooled sensitivity of 43.1% (95% CI 22.5 to 66.4%) for this technique.

Low or moderate quality evidence from 9 cross-sectional evaluations in 2828 children and young people (under the age of 15) with suspected pulmonary TB comparing NAATs with a culture-based reference standard showed NAATs to have a pooled sensitivity of 71.3% (low quality evidence), though there was considerable uncertainty in the estimates (95% CI 54.3 to 83.8%), and a pooled specificity of 98.6% (95% CI 98.0 to 99.1%) (moderate quality evidence).

Very low quality of evidence from 1 cross-sectional evaluation in 362 children and young people with suspected pulmonary TB comparing IGRAs with a culture-based reference standard showed IGRAs to have a sensitivity of 79.7% (95% CI 72.7 to 86.7%) and a specificity of 16.7% (95% CI 11.9 to 21.4%).

Very low quality of evidence from 1 cross-sectional evaluation in 362 children and young people with suspected pulmonary TB comparing TSTs with a culture-based reference standard showed TSTs to have a sensitivity of 89.8% (95% CI 84.6 to 95.1%) and a specificity of 5.1% (95% CI 2.3 to 8.0%). A second evaluation in 110 children and young people with suspected pulmonary TB showed TSTs to have a sensitivity of 47% and a specificity of 60%; no confidence intervals were provided.

Patient who are culture negative

No evidence was identified.

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3.3.51 Health economic evidence

An economic evaluations filter was applied to the search protocol, and 2263 papers were returned from the searches. Of these papers, 2228 were excluded on the basis of title/abstract sifting, and 35 papers were retrieved for full-text sifting. Of these, 33 papers were excluded upon review, and 2 CUAs were included.

Hughes et al. (2011) used a Markov model to simulate a theoretical cohort of patients with an NHS & PSS cost perspective. They present 10 different possible diagnostic strategies to compare the cost effectiveness of nucleic acid amplification techniques (NAAT) with sputum smear microscopy (SSM) and culture, detailed as follows:

1. SSM followed by culture when SSM negative
2. SSM followed by culture every time
3. SSM and NAAT, culture when discrepancy between results
4. SSM and NAAT when SSM negative, otherwise culture
5. SSM and NAAT when SSM positive, otherwise culture
6. NAAT only
7. NAAT followed by culture every time
8. NAAT and culture when NAAT positive
9. NAAT and culture when NAAT negative
10. SSM and NAAT followed by culture every time

In the base-case analysis, strategies using NAATs had ICERs in excess of £20,000/QALY and were not considered cost effective. The most cost-effective strategy was SSM followed by culture on all specimens collected (ICER = £9,748 per QALY). A deterministic sensitivity analysis found that the model is sensitive to inputs of pre-test prevalence, NAAT costs, and the time taken to detect a false-negative diagnosis. In high-prevalence settings, where there is a higher probability that the patient undergoing testing will have TB, NAAT may be cost effective for routine use alongside SSM. When the time to diagnosis of a false-negative case is decreased to the short time of 10.4 weeks, strategy 1 (SSM followed by culture when SSM positive), as the lowest cost option, becomes the optimal choice. By reducing the costs of NAAT to £42.66, strategy 6 (SSM and NAAT when SSM negative, otherwise culture) becomes cost effective. At any other price above that, strategy 3 (SSM followed by culture every time) remains the most cost-effective option. The analysis did not consider the effect that early diagnosis of TB using NAAT might have on prognosis and any downstream savings and benefits that may result from it. Likewise the impact of diagnostic strategies on the onward transmission of TB was not explored.

In a US-based study, Choi et al. (2013) compared standard diagnostics (3 x sputum + liquid culture, chest radiograph, DST on positive culture) with 2 molecular tests – amplified MTD and Xpert MTB/RIF on 1 sputum sample used either selectively (smear-positive only) or intensively (regardless of smear status). The costs for staffing, laboratory testing equipment, inpatient stay and medications were taken from a single laboratory case study, and therefore are unlikely to be generalisable to the NHS. The study also relies on quality of life parameters drawn from expert clinical opinion. At the time of the study, the pricing of Xpert MTB/RIF was uncertain, although this was explored in the sensitivity analysis.

In the base-case analysis, using a maximum ICER threshold of $50,000 per QALY, the no-molecular testing strategy was dominated by all strategies that included molecular testing. Replacing MTD with Xpert was also found to be cost effective. Compared with strategy 2 (‘selective MTD’), strategy 4 (‘selective Xpert’) was associated with an ICER of $23,111 per QALY gained. Strategy 5 (‘intensive Xpert’) compared with strategy 3 (‘intensive MTD’) had an ICER of $16,289 per QALY gained.

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In one-way sensitivity analysis, the 'intensive' Xpert strategy dominated the strategy without molecular testing (strategy 1) except when cost per Xpert test rose above $475 or Xpert specificity was lower than 96%. For outpatient evaluations, 'intensive' Xpert was cost-effective compared with strategy 1 (ICER $16,900 per QALY gained). For inpatient evaluations, 'intensive' Xpert dominated strategy 1 (owing to consequentially reduced costs for inpatient stay, isolation, etc.).

A probabilistic sensitivity analysis suggested that the 'intensive' Xpert algorithm was cost effective in more than 99% of simulations compared with diagnostic algorithms without molecular testing (assuming QALYs are valued at $50,000). Compared with existing molecular assays (MTB), Xpert was considered cost effective with an ICER of $39,992 per QALY gained. The authors did not consider the costs of transmission, but stated that any consideration of transmission is likely to increase cost effectiveness of molecular methods as cases are detected earlier.

3.3.64 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that diagnostic test accuracy and time to diagnosis or treatment initiation were the most critical to decision making. The aim of diagnosing tuberculosis is the provision of information to guide decisions about a patients' care; for example, the decision whether to initiate treatment or not, changes to care based on suspicion of drug resistance, the need for isolation, and so on. One of the key features of a desirable test is that results are accurate. The GDG noted that, in practice, there is a trade-off between sensitivity and specificity for many tests. Although the GDG would prefer to recommend tests that perform well on both measures, on discussing their relative importance the group felt that sensitivity, and the capacity of highly sensitive tests to rule out disease, was more important to their decision-making. The GDG also considered the accuracy that they would consider to be 'acceptable' in a test, and specified a threshold for sensitivity of 70% and a threshold for specificity of 95%. Specificity was set at a particularly high threshold because tests for tuberculosis are known to be highly specific, and therefore accepting anything below this is not necessary Another key feature of a desirable test is that results are available more rapidly than those of the reference standard, culture. Diagnostic delay can have a number of detrimental consequences – delay to the initiation of appropriate treatment, disenfranchisement of the patient through unnecessary treatment or isolation, or through a lack an adequate diagnosis or information. Delays to diagnosis may mean delays to treatment initiation, which may in turn lead to greater risks of morbidity (both long- and short-term) and mortality. Delays of up to 2–3 weeks in the treatment of patients with active TB are common; longer delays frequently occur and delayed diagnosis is usually an important contributory factor in fatal cases of TB in the UK. Alternatively, it may mean that clinicians do not wait for a confirmation of diagnosis, and unnecessarily put individuals who do not have active tuberculosis on antituberculosis regimens, which carry a risk of adverse events. Delays to diagnosis may also mean that people with infectious active pulmonary tuberculosis are not isolated, causing a continued risk to others. Alternatively, it may be that clinicians are overly cautious and decide to isolate a person, who later proves to be disease-free, without a confirmed diagnosis; the group were concerned that such occurrences may make individuals wary of approaching health services for diagnosis and treatment. Such delays can arise through delays between the initiation of diagnostic efforts and the achievement of a test result, whether through issues relating to technical features of the test, or through issues relating to the organisation and delivery of the service, or through delays in the clinicians obtaining a specimen. This review considered the degree to which a delay can be minimised through the use of more rapid tests; service delivery and encouraging more prompt

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	acquisition of samples are not considered here. The prognostic value of tests was also considered important for decision-making, as were the acceptability of approach to the patient or clinician and the incidence of adverse events associated with different diagnostic approaches, though these outcomes were not considered critical. Despite this, no data on these outcomes was identified in the included papers.
Trade-off between benefits and harms	Ideally, conducting a diagnostic test would precisely identify all the people with the disease, so that they can receive appropriate care, and similarly correctly identify all patients who are disease free. In other words, a diagnostic test would ideally have a high sensitivity (a small proportion of false negatives compared to true positives) and a high specificity (a small proportion of false positives compared to true negatives). False negatives mean that people with active disease may not receive appropriate treatment and may be at considerable risk of morbidity and mortality as the disease advances. They also mean that those with infectious disease are not identified, creating a risk from infection to those around them. Alternatively, a false positive may mean that an individual undergoes unnecessary treatment or isolation, which may both have a significant impact on that person's quality of life. **Trade-off between benefits and harms in adults** <u>Sputum smear microscopy</u> On review of the evidence for sputum smear microscopy, the GDG noted that as a standalone test it did not, although close, quite meet the agreed minimum threshold for sensitivity, nor did the 95% confidence interval for the estimate cross it (65.6% (95% CI 61.1 to 69.9%)). The group also noted that microscopy does not detect viable, disease-causing bacilli alone, but may also detect 'dead', non-viable bacilli. Furthermore, microscopy is not specifically a test for M. tuberculosis, rather it detects acid-fast bacilli (AFB) more generally. For this reason, location of study may be important: for studies conducted in areas with a high ratio of tuberculous to nontuberculous mycobacteria, there can be greater confidence that the AFB detected is M. tuberculosis. Attempts were made to maximise confidence by classifying data for nontuberculous mycobacteria as negative, where sufficient data was provided in the study reports (that is, where AFB had been confirmed as tuberculous or nontuberculous by additional testing). However, although this maximises confidence that AFB detected is M. tuberculosis, and therefore cases that are classified as positive are true positives, it does not reflect the real world. The evidence shows microscopy to be good at detecting M. tuberculosis in an 'ideal world', but in the real-world UK context some cases classified as AFB-positive would not actually be M. tuberculosis. Despite these shortcomings, the group noted that microscopy performed well on specificity. Additionally, when the sensitivity data was viewed for fluorescence microscopy alone (the preferred smear technique, according to Public Health England's Standards for Microbiology Investigations), the threshold was very nearly met, with the upper 95% confidence interval comfortably above (69.2% (95% CI 62.7 to 75.1%)). Microscopy is also considerably faster than culture. Therefore, the GDG felt that, on balance, there was not sufficient evidence to remove microscopy from the diagnostic pathway, and that microscopy is still a useful investigation alongside other tests. Only 3 studies were identified that investigated the use of microscopy in the HIV-positive subgroup. Although microscopy performed poorly in the limited data for sensitivity in people with HIV, the GDG did not feel there was sufficient data to make specific recommendations for the use of microscopy in this subgroup. No studies were identified that reported microscopy data for people who are HIV-negative. <u>Chest x-ray</u> Although no data was identified that investigated chest x-ray alone, the group felt that a posterior-anterior chest x-ray is a useful preliminary test for

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establishing suspicion of TB disease. This has been standard practice for many years and the group felt that it should continue to be so. Posterior-anterior chest x-rays had been useful diagnostic tools in their clinical experience, helping to indicate the presence of active TB and its extent, and through assisting other diagnostic efforts (for example, guiding sample collection).

However, the GDG also noted that a chest x-ray may also show signs of past infection and therefore TB cannot be diagnosed with certainty from a chest x-ray alone. Suspicious chest x-rays should be followed and interpreted in accordance with other tests, in particular microbiological investigations.

NAATs

In determining the usefulness of NAATs that are able to identify both M. tuberculosis and drug resistance, the GDG noted that considering the TB identification component of the test's functionality in isolation was of limited use. They felt that the 2 functions are intrinsically linked, particularly with regard to the cost-effectiveness of the tests.

Although there was between-study variation, pooled estimates for sensitivity and specificity were relatively consistent, with NAATs performing well overall on both measures. The GDG felt that important distinctions in the usefulness of each NAAT may be driven by more practical considerations, such as timeliness (impacts on infection control and treatment outcome), ease of use, amount of specimen required, and so on, although no data was available for these.

Although the data for NAATs was broken down by the specific test used, the group felt it was important that any guidance issued on the use of NAATs should not be over-prescriptive with regard to the specific test or type of test that should be used. This is because the field of rapid diagnostic NAATs is fast-moving, and may have moved on before this guidance is reviewed. The aforementioned consistency of pooled test accuracy and lack of other discriminators supports the GDG's decision not to recommend a specific NAAT or type of NAAT.

With the good pooled sensitivity achieved (89.0% (95% CI 87.2 to 90.6%)), and the comparable rapidity of NAATs to microscopy, the group felt that NAATs may make a useful addition to the current diagnostic pathway in patients in whom TB is suspected and for whom the results may alter care. That is, as an addition to microscopy in patients with disease suspected by, for example, chest x-ray whilst the results for culture are awaited. Suspicion of disease was considered an important prerequisite for test use as all evidence identified used this as a criterion for inclusion, and therefore this requirement reflects the evidence base and ensures that the test is only used where it can add the most value.

A particularly notable population for whom the GDG felt that NAATs may be useful are people with HIV, as the sensitivity of microscopy was particularly poor in this population (40.8% (95% CI 18.6 to 67.6%)) whereas the sensitivity of NAATs met the agreed minimum threshold (80.9% (95% CI 72.9 to 86.9%)). No evidence was identified for other immunocompromised people; however, the group felt that it may be appropriate to extrapolate evidence from the HIV-positive subgroup. This is because, in their experience, microscopy performs very poorly with regards to sensitivity (that is, results in a high proportion of false negatives to true positives) in this population as well. As with people who are HIV-positive, the threshold for clinical suspicion of disease is also much lower in these patients. It may therefore be appropriate to perform NAATs in other immunocompromised people as well.

Other populations for whom the GDG felt NAATs may be useful were those for whom rapid confirmation of TB will alter their care – this may include confirmation of the presence or absence of nontuberculous AFB in smear-positive patients, or the confirmation of drug susceptibility, and the subsequent impact such confirmations will have on treatment decisions, decisions relating to isolation, and so on. NAATs may also hold value in situations in which a large contact-tracing initiative is being considered. The aim being to avoid starting large exercises until you know the potential source person has TB.

The group discussed the favourable sensitivity and specificity achieved by NAATs in smear-negative patients (72.6% (95% CI 68.1 to 76.8%) and 98.6%

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(95% CI 97.9 to 99.0%), respectively). However, smear-negative patients represent a very large group and recommending the use of NAATs in all smear-negative patients would have significant resource implications, placing significant burden upon laboratories conducting NAATs. Therefore, the GDG decided that NAATs would not be routinely recommended in smear-negative patients (unless they fulfil one of the other criteria for NAAT use). This is supported by the high specificity of microscopy; that is, there is a high level of confidence that a smear-negative patient is a true negative.

Phage-based tests

The group noted that the specificity of phage-based tests was uniformly high across all five studies (ranging from 97 to 99%), but sensitivity estimates were much lower and more variable (ranging from 27 to 88%). The group felt that this variation in sensitivity may have been related to several factors. Firstly, the nature of the test requires a significant amount of accuracy and skill in its conduct. The second reason is biological, relating to the stability of the phage and the interaction of the two living biological systems (the phage and the mycobacteria). This variability in the sensitivity, along with the fact that only five studies were available, limited the conclusions that could be drawn. The group did not feel that the evidence provided a sufficient basis from which to make a recommendation concerning the use of phage-based tests.

IGRAs

The GDG felt that IGRAs are often used too bluntly in practice. That is, because of their ease of use, a positive IGRA along with, for example, a persistent cough has in the past led clinicians to start patients on treatment for active disease, without obtaining other supporting evidence. Although this is rare, it is a misuse of the test and means that patients without active TB must continue treatment for no personal benefit.

The key problem with their use is that they detect latent infection, and not only active disease. The GDG noted the good sensitivity of IGRAs (89.3% (95% CI 83.4 to 93.3%)); however, although the group felt that they may be useful as part of the holistic diagnosis of active TB, the evidence was not strong enough to support a recommendation for their routine use.

TSTs

The 2 studies identified that assessed the use of TSTs for the diagnosis of active TB showed the test to have very poor and very variable sensitivity (46.1% (95% CI 12.1 to 84.2%)). The group did not feel there was a place for TST in the routine diagnosis of active TB, though its use in the diagnosis of latent infection may mean that it can be part of the clinical picture that, alongside for example chest x-ray or patient history, leads to a clinical suspicion of TB, thus initiating diagnostic efforts to identify or rule out active disease.

Antibody-based tests

The GDG felt that the low and variable sensitivity of antibody-based tests precluded their inclusion in the standard diagnostic pathway for active pulmonary disease.

Trade-off between benefits and harms in children and young people

Sputum smear microscopy

On review of the evidence for sputum smear microscopy in children, the GDG noted that although the test performed well for specificity, it performed poorly with regards to sensitivity. At a pooled sensitivity of 56.3%, microscopy far short of the 70% threshold for acceptability. Furthermore, when the sensitivity data was viewed for fluorescence microscopy (the preferred smear technique, according to Public Health England's Standards for Microbiology Investigations) alone, sensitivity fell even further below the threshold for acceptability to just 43.1%. The GDG also noted, however, that this was perhaps unsurprising given

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the lower bacterial load expected in younger children (the majority of included participants were under the age of 5).

Despite this, the group did not feel that there was sufficient evidence to remove microscopy from the diagnostic pathway, and that microscopy is still a useful investigation in children alongside other tests. For example, NAATs should be used to confirm smear-negative results due to the low sensitivity of microscopy in children.

No evidence was found explicitly investigating the diagnostic accuracy of sputum smear microscopy by HIV status.

Chest x-ray

Only limited evidence was identified with regards the diagnostic accuracy of chest radiography – one cross-sectional study of 110 participants. Although the sensitivity of the test was good (72%), the specificity was low (54%).

The group did not feel that there was evidence to support the removal of chest x-ray from the diagnostic pathway. No confidence intervals were available to assess the accuracy of the estimates of effect, and the population only covered those aged 5 years and under. Additionally, the group had also found x-ray to be a useful component of a holistic approach to diagnosis in their own clinical experience.

NAATs

The group emphasised in their discussions that, due to the particularly severe consequences of leaving the disease untreated, it is desirable to start treatment as rapidly as possible in children with tuberculosis. For this reason, the reduced time to diagnosis, and therefore initiation of treatment, associated with the use of NAATs supports the routine use of these tests as part of a package of tests. However, although they have good sensitivity in comparison to other routinely used tests, such as microscopy and chest x-ray, the sensitivity of NAATs is not perfect, and the group therefore felt that a negative NAAT result should not by itself lead to withdrawal of treatment, rather it should be considered alongside the results of the other tests.

Four studies allowed the diagnostic accuracy of NAATs to be assessed in children and young people with suspected pulmonary tuberculosis who were coinfected with HIV. The pooled sensitivity and specificity both met the agreed threshold of acceptability, although the confidence intervals of the pooled sensitivity were both wide and crossed this threshold.

When the use of NAATs to diagnose pulmonary tuberculosis in children and young people who are HIV-negative was assessed, the 4 studies provided a pooled sensitivity that did not quite meet the threshold for acceptability. However, the group did not feel this was sufficient grounds on which to preclude the use of NAATs in this population.

IGRAs

The GDG noted that although the specificity of IGRAs was very poor (16.7%), the sensitivity was very high (79.7%). Although, as with the other tests discussed here, the diagnostic accuracy is not sufficient to recommend its use as a standalone test, its combination with other tests, in particular those tests with a low sensitivity but high specificity for which an IGRA may be useful in confirming a negative result, may be improve the overall accuracy of the diagnostic pathway.

The group also discussed 2 papers that failed to meet inclusion criteria – as neither reported the specificity of the – but which they felt constituted informative, supportive evidence. The first, Bamford et al (2010)[s] , collected data

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s *Bamford AR, Crook AM, Clark JE, Nademi Z, Dixon G, Paton JY, Riddell A, Drobniewski F, Riordan A, Anderson ST, Williams A, Walters S, Kampmann B (2010) Comparison of interferon-gamma release assays and tuberculin skin test in predicting active tuberculosis (TB) in children in the UK: a paediatric TB network study. Arch Dis Child 95(3):180-6*

	on IGRAs (at least one of the commercially available IGRAs, T-SPOT.TB or Quantiferon-Gold in Tube) performed in 333 children aged between 2 months and 16 years from at six large paediatric centres around the UK, and compared them against a culture-based reference standard. The second paper, Kampmann et al (2009)[t] , collected data on IGRAs (again, at least one of the commercially available IGRAs, T-SPOT.TB or Quantiferon-Gold in Tube) performed in 209 children of the same age bracket, again from the UK and again against a culture-based reference standard. The first study reported a T-SPOT.TB sensitivity of 67% (95% CI 46 to 83%) and a Quantiferon-Gold in Tube sensitivity of 78% (95% CI 64 to 89%), the second of 58% and 80%, respectively. The GDG felt that this UK data, particularly that for the Quantiferon-Gold in Tube assay, supported the conclusion drawn from the single included study that IGRAs may have value in boosting the sensitivity of other tests. The group noted, however, that further research in this area, particularly with regards to combinations of tests, would be useful to future decision-making.[u] TSTs The GDG observed that the estimates for the sensitivity and specificity of TSTs varied considerably between the 2 included studies. The 2 additional studies noted above – the 2 UK studies reporting sensitivity data for IGRAs – also reported data for TSTs. Bamford et al (2010) reported a sensitivity of 82% (95% CI 68 to 92%) for TSTs with an induration threshold of 15 mm. Kampmann et al (2009) reported a sensitivity of 83% for TSTs with an induration threshold of 15 mm and 88% for an induration threshold of 10 mm. Again, the group felt that this additional, UK-based data supported the use of TSTs where the low sensitivity of other tests may warrant further diagnostic information. Phage-based tests No evidence was found explicitly investigating the diagnostic accuracy of phage-based tests in children and young people. Antibody-based tests No evidence was found explicitly investigating the diagnostic accuracy of antibody-based tests in children and young people.
Trade-off between net health benefits and resource use	The GDG felt examining the cost-effectiveness of NAATs and molecular tests to diagnose TB separately from their ability to detect drug resistance was of limited use.The GDG considered the health economic evidence from the systematic review alongside the NIHR funded health technology assessment discussed in section 5.3, which incorporates the use of rapid tests for both TB diagnosis and DST in the health economic model. The GDG noted that the reccomendations concerning SSM, TST and culture and CXR were unlikely to incur additional resource impacts as these are low cost and widely used.
Quality of evidence	No evidence was identified for those who are culture negative. **Quality of the evidence in adults** The quality of evidence for many tests/outcomes suffered from poor reporting. Commonly unreported features included methods for the selection and enrolment of patients, the use of blinding, thresholds used for test interpretation and population characteristics (including age). Errors in the design or reporting of TB diagnostic studies were common, including failure to describe methods, such as those for the selection and

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t *Kampmann B, Whittaker E, Williams A, Walters S, Gordon A, Martinez-Alier N, Williams B, Crook AM, Hutton AM, Anderson ST (2009) Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. Eur Respir J 33(6): 1374-82*

enrolment of patients, lack of blinding, inadequate sample size, and inadequate gold standards for clinical case definition. Furthermore, sensitivity and specificity values are often calculated in different ways, either on a patient basis or a specimen basis.

Where reported, many elements of study design also impacted the quality of the evidence. Firstly, many studies did not use a consecutive or random sample, introducing a potential source of selection bias. Secondly many of the studies were unblinded. The interpretation of most diagnostics involves a degree of subjective interpretation. This can be influenced by both the knowledge of any other tests conducted, the reference standard in the interpretation of the index test, and vice versa, and the characteristics of the individual tested. Blinding would have reduced this potential source of bias, although for many of the diagnostic tests discussed here it may not be crucial as the same samples are often used for index tests and reference standards, and most are subject to standardised laboratory procedures and definitions.

Another issue that regularly contributed to the poor quality of the evidence was the reference standard used. The analysis of diagnostic test accuracy using measures such as sensitivity and specificity assumes that the reference standard used is as close to 100% accurate as it can be. However, in the case of TB, the available test is far from perfect, particularly in children and people who are immunocompromised, such as those with HIV. Culture may fail to detect M. tuberculosis that is picked up by other tests, such as NAATs, for example, and will therefore mistakenly classify patients with TB as false-positives. Serious inaccuracies in the reference standard may lead to over- or underestimation of the true accuracy of a diagnostic test.

In addition to the reference standard being imperfect, there is the issue of different reference standards being used across studies, introducing a source of heterogeneity. It may be that different culture techniques were used (for example, solid versus liquid), or that additional tests or criteria were used in conjunction with the culture, such as microscopy, histology, x-ray or treatment response. This means that studies are not comparing ‘like’ with ‘like’, and therefore sensitivities and specificities are judged by different measures.

With regards to the generalisability of the evidence to the UK context, it was notable that none of the studies identified were performed in the UK. Test methods, such as those used for processing the specimens or the method of isolating cultures, may differ in various settings, meaning that the index tests and reference standards may not all be the same as those employed in UK settings. Another issue relating to the generalisability of the evidence to the UK context was that a significant number of studies were conducted in high incidence countries (that is, countries/territories with an estimated incidence rate of greater than, or equal to, 40 per 100,000, as defined by Public Health England). With an estimated incidence of 13.9 per 100,000, the epidemiology of TB in the UK is not equivalent. Further to this, the lack of information regarding population characteristics and patient selection criteria in many studies meant that there could be limited assessment of the populations’ applicability to the current UK context.

With regards to the age of participants, a number of studies included a small proportion that were under 18 years old or provided no details of the age of the study population. Although important to note, it is not anticipated that this will significantly affect the results.

No data was identified for the prognostic value of tests the acceptability of approach to the patient or clinician and the incidence of adverse events, all of which were identified by the GDG as potentially useful to their decision-making. Additionally, information regarding the time to diagnosis or treatment initiation of each test was rarely a formal outcome.

Quality of the evidence in children and young people

As with the adult population, no data was identified for the prognostic value of tests the acceptability of approach to the patient or clinician and the incidence of adverse events, all of which were identified by the GDG as potentially useful to

	their decision-making. Additionally, no further information was identified with regards to the time to diagnosis or treatment initiation, although this will be comparable to the limited data identified in adults. There was a paucity of data for the HIV subgroups, such that the GDG did not feel able to make specific recommendations for HIV-positive and HIV-negative populations. Specimens used were generally induced sputum or gastric aspirate or lavage. Limited data was available for spontaneously produced specimens, which is the preferred diagnostic sample. Again, as with the evidence base for adults, errors in the design or reporting of the studies were common, including failure to describe methods (such as those for the selection and enrolment of patients), lack of blinding (or a failure to report the use or not of blinding), inadequate sample size, and inadequate and varied gold standards for clinical case definition.
Other considerations	Although the evidence for individual tests was considered in isolation, in reality test results would not be considered in isolation but would contribute to the overall evidence on which a diagnosis is made. At numerous points in the discussion, the GDG noted that a diagnosis of TB is built from a combination of context, symptoms, clinical signs and investigations. The diagnosis is rarely made from a single piece of evidence, and the sensitivity and specificity of individual tests may not reflect the strength of multiple tests or data. This can be true for all patients, but is particularly true in children and in people who are immunocompromised, such as those with HIV. Given the low sensitivity of tests in children, it can be hard to rule out a disease based on the results of a single test. The GDG therefore stressed that the use of multiple tests concurrently is important. Additionally, the GDG also felt that any test results should be interpreted in light of more general information obtained through history taking and clinical examination. However, they also noted that this holistic approach requires experience and skill, and that a team with appropriate experience in diagnosing paediatric tuberculosis should be involved. No data was found for children and young people aged over 15 and under 18. However, the GDG felt that pulmonary disease presents in a similar manner as for adults in these older children, as well as being comparable with regards bacterial load. Therefore the group felt that diagnosis of pulmonary tuberculosis in this population should be as for adults. Despite wide between-study variation in the estimates of sensitivity, the GDG noted that NAATs met the thresholds for acceptability for both sensitivity and specificity. It was the only test to do so. For this reason, and given the limited sensitivity and/or specificity of the other tests for which data were available, the group felt that NAATs would be a useful addition to the diagnostic pathway for pulmonary tuberculosis in children. The group felt it important to note that, when the analyses were unpicked by age, NAATs performed poorly in under-10s but well in teenagers (10 to 15 years). Again, it was thought that this observation would have resulted from the higher bacterial load observed in older children and young people. Despite this, the fact that the estimate of effect for those aged under 10 was based upon a single study, and just 2 studies for those aged 10 to 15, meant that the group did not wish to translate this observation into recommendations specific to each of these age groups.

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3.3.7 Recommendations

28. If TB is a possibility, microbiology staff should consider carrying out TB culture on samples, even if it is not requested. [2006, amended 2015]

29. **If there are clinical signs and symptoms consistent with a diagnosis of TB, start treatment without waiting for culture results. [2006]**

30. **Consider completing the standard recommended regimen, even if subsequent culture results are negative. [2006, amended 2015]**

Pulmonary TB

31. **Take a posterior-anterior chest X-ray; do further diagnostic investigations (as detailed below and summarised in table 1) if chest X-ray appearances suggest TB. [2015]**

32. **Send multiple respiratory samples (3 deep cough sputum samples, preferably with 1 early morning sample) for TB microscopy and culture. [2015]**
    - This should be before starting treatment if possible, or, failing that, within 7 days of starting treatment in people with life-threatening disease. **[2006, amended 2015]**
    - Obtain spontaneously-produced, deep cough sputum samples if possible, otherwise use:
        - 3 gastric lavages or 3 inductions of sputum in children and young people **[new 2015]**, or
        - induction of sputum or bronchoscopy and lavage in adults. **[2006, amended 2015]**
    - Laboratory practices should be in accordance with Public Health England's Standards for Microbiology Investigations. **[new 2015]**

33. **Send samples for TB culture from autopsy samples if pulmonary TB is a possibility. [2006]**

Adults

34. **A TB specialist should request rapid diagnostic nucleic acid amplification tests for the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*) on primary specimens (listed in table 1) if there is clinical suspicion of TB disease, and:**
    - the person has HIV, or
    - rapid information about mycobacterial species would alter the person's care, or
    - the need for a large contact-tracing initiative is being explored. [new 2015]

Children and young people

35. **In children and young people aged 15 years or younger with suspected pulmonary TB, offer rapid diagnostic nucleic acid amplification tests for the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*). Usually only 1 nucleic acid amplification test will be necessary per specimen type (for example, spontaneous sputum, induced sputum or gastric lavage). (Listed in table 1). [new 2015]**

Table 1: Diagnostic investigations for pulmonary TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)

Pulmonary (adult)	Posterior-anterior X-ray	3 adequate respiratory samples: • preferably spontaneously-produced, deep cough sputum samples, otherwise induced sputum or bronchoscopy and lavage • preferably 1 early morning sample	Microscopy Culture Histology	Nucleic acid amplification test
Pulmonary (young people aged 16–17 years)	Posterior-anterior X-ray	3 adequate respiratory samples: • preferably spontaneously-produced, deep cough sputum samples, otherwise induced sputum or gastric lavage • preferably 1 early morning sample	Microscopy Culture Histology	Nucleic acid amplification test
Pulmonary (children aged 15 years or younger)	Posterior-anterior X-ray	3 adequate respiratory samples: • preferably spontaneously-produced, deep cough sputum samples, otherwise induced sputum or gastric lavage	Microscopy Culture Histology Nucleic acid amplification tests (1 per specimen type)	Interferon-gamma release assay and/or tuberculin skin test (with expert input)

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		• preferably 1 early morning sample		

36. In young people aged 16–18 years use the same criteria as in adults to decide whether to request rapid diagnostic nucleic acid amplification tests (see table 1). [new 2015]

37. Either a paediatrician with experience and training in the treatment of TB or a general paediatrician with advice from a specialised clinician should investigate and manage TB in children and young people. [new 2015]

38. An expert in paediatric TB may request interferon gamma release assays and tuberculin skin tests. Interpret these together with other diagnostic tools (such as history taking, clinical examination and imaging). [new 2015]

3.3.8 Research recommendations

2. In people with suspected TB, what is the relative clinical and cost effectiveness of a universal approach compared to a risk-based approach to using rapid nucleic acid amplification tests?

Why this is important

The GDG noted that there were 2 possible approaches to using rapid nucleic acid amplification tests for suspected TB. The current approach is to use them only if TB is strongly suspected and rapid information about mycobacterial species would alter the person's care. Another approach is to use them in anyone with a possible diagnosis of TB. There is a trade-off between ensuring that all people with active TB are diagnosed and avoiding a large number of false positives, which lead to unnecessary treatment. This trade-off may lead to differences in the cost effectiveness of each approach. NICE's systematic review of the diagnosis of active TB did not identify any robust evidence on this, nor did the health technology assessment on using nucleic acid amplification tests to detect drug resistance. Cost-effectiveness studies are needed to improve understanding in this area.

3. Is it more cost effective to organise rapid diagnostic services in local or centralised laboratories?

Why this is important

The relative clinical and cost effectiveness of rapid diagnostic tests may be heavily influenced by whether the services delivering them are arranged locally or in centralised laboratories. The organisation of laboratory services may affect the time taken to start appropriate treatment, with subsequent effects on morbidity and mortality rates. In terms of cost effectiveness, there is a balance between these factors and the relative costs of providing localised and centralised services. UK-based cost-effectiveness studies are needed to improve service organisation.

4. How accurate, effective and cost effective are point-of-care diagnostics?

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Why this is important

Point-of-care diagnostics may shorten the time between suspicion of disease or drug resistance and starting appropriate treatment. However, NICE identified no evidence in this area. The diagnostic accuracy of these tests should be compared with those currently used, in cross-sectional and cost-effectiveness studies, to determine whether they have a place in UK practice. Outcomes should also include time waiting for results and the cost effectiveness of the tests.

5. Apart from culture, what other diagnostic tests or combinations of tests are effective in establishing an accurate diagnosis of active respiratory TB in children and young people with suspected active TB?

Why this is important

The Committee noted the paucity of evidence on the diagnosis of active TB in children. The disease manifests differently in children than in adults, and more evidence would have been useful to the Committee. Cross-sectional studies are needed to examine the relative accuracy of different tests, and the most appropriate specimen type for these tests, compared with those currently in use. In particular, the poor accuracy of many tests in children means that diagnostic strategies – that is, combinations of tests – should be investigated, including both tests with high sensitivity and those based on host response.

6. In people with suspected TB disease, which fluid or tissue samples provide the highest accuracy in nucleic acid amplification tests?

Why this is important

In order to maximise the accuracy of nucleic acid amplification tests in the diagnosis of active TB disease, the GDG felt that additional information regarding the type of optimal specimen – tissue compared to fluid – would have been useful to their decision-making. The reviews conducted found only limited evidence for this. Cross-sectional studies of nucleic acid amplification tests using linked specimens – that is, tissue and fluid specimens taken from and compared in the same person – should be conducted.

3.4 Diagnosing active pulmonary tuberculosis: collecting respiratory samples

3.4.1 Clinical introduction

As discussed above in section 3.3, current strategies to investigate patients presenting with suspected pulmonary tuberculosis use a variety of tests, including microscopy and culture, to establish a diagnosis. Specimen collection is a key element of investigations, and for pulmonary tuberculosis respiratory tract specimens are required. Spontaneously produced sputum is thought to be the best specimen, but spontaneous production of sputum is not always possible. It is particularly rare in young children. For this reason, in people who cannot produce sputum spontaneously, various options (sputum induction, nasogastric aspiration (with and without lavage), nasopharyngeal aspiration, bronchoalveolar washings taken during bronchoscopy, laryngeal swabs and lung puncture aspiration) are possible approaches to aid sample collection.

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3.4.2 Adults [2006, amended 2015]

3.4.2.1 Methodological introduction

Studies were identified which calculated the sensitivity, specificity or predictive value of respiratory samples when compared with culture as the gold standard for the diagnosis of pulmonary TB. Studies on sputum smear microscopy were excluded from review if they were conducted in non-Organisation for Economic Co-operation and Development countries as it was thought that in terms of background levels of mycobacteria and laboratory standards they might not be representative of the UK.

Generally studies were unblinded (mostly because they were retrospective analyses). Blinding, however, is probably not crucial to avoid bias in the assessment of smear microscopy as the same samples are used for smear and culture and are subject to standardised laboratory procedures and definitions. It was notable that none of the studies identified were performed in the UK.

3.4.2.2 Evidence statements

The rates of smear positivity were calculated for specimens of expectorated sputum, induced sputum and bronchoalveolar lavage (BAL) specimens in a study in the USA. Findings of smears of expectorated sputum specimens showed that 55% were culture positive for M. tuberculosis and were AFB smear positive. Smear positivity rates for induced sputum were 38% and for BAL were 26%. When the predictive value was calculated by including only the first smear-positive specimen from each patient the values were 87% for expectorated sputum, 70% for induced sputum and 71% for BAL. **(2)**

3.4.3 From evidence to recommendations

The yield of positive sputum microscopy is improved by an adequate sputum sample (5 ml or more), concentration of sputum, analysing multiple samples, and by fluorescence microscopy as the screening tool. Smear positive rates are higher for spontaneously induced sputum than for either induced sputum or BAL samples. The positive predictive value of positive sputum microscopy is 92% for spontaneously produced sputum, and 71% for both BAL and induced sputum. There appeared to be little difference in the results between HIV-positive and HIV-negative patients in terms of bacteriological results and sputum smear positivity. Gastric washings are less likely to provide useful material in adults, because of acidic inhibition.

3.4.4 Children

3.4.4.1 Review question B

What is the most effective method of collecting respiratory samples from children unable to expectorate spontaneously?

3.4.4.2 Evidence review

This review aimed to establish which approach to sputum collection is the most acceptable to children unable to produce a sample spontaneously, as well as to their parents or carers and those performing the procedures, and also to identify the most effective in establishing an accurate diagnosis of pulmonary tuberculosis.

For this review question, papers were identified from a number of different databases (Embase, Medline, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database). A focused search strategy was

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used to pull in all studies that compared differing approaches to collecting sputum samples in children and young people (<18 years) with suspected pulmonary tuberculosis. Randomised, quasi-randomised and non-randomised controlled trials were considered for inclusion, as were cohort studies and case-control studies. Trials were excluded if:

- adults (aged 18 or over) were included;
- they were case studies, case series and narrative reviews.

From a database of 2492 abstracts, 131 full-text articles were ordered and 22 papers met the inclusion criteria. The majority of the identified studies were cross-sectional in design, though 2 randomised controlled trials were also identified.

All recommendations were made using the recommendations made in the previous guideline (CG117) as a starting point.

3.4.4.3 Evidence statements

Very low quality of evidence from 2 cross-sectional evaluations in 420 children and young people with suspected pulmonary tuberculosis showed nasogastric aspiration with lavage to have a higher cumulative culture positivity over 2 specimens than sputum induction (OR 2.24 (95% CI 1.63 to 3.09). Additionally, very low quality of evidence from 1 cross-sectional evaluation in 403 children and young people with suspected pulmonary tuberculosis showed nasogastric aspiration/lavage to have a higher cumulative smear positivity over 2 specimens than sputum induction (1.92 (95% CI 1.13 to 3.26). However, very low quality of evidence from 2 cross-sectional evaluations in 267 children and young people with suspected pulmonary tuberculosis also showed no significant difference between nasogastric aspiration with lavage and sputum induction with regards cumulative culture and smear positivity over 3 specimens (OR 0.74 (95% CI 0.48 to 1.15) and 0.64 (95% CI 0.34 to 1.2), respectively).

Very low quality of evidence from 3 cross-sectional studies in over 1650 specimens from children and young people with suspected pulmonary tuberculosis showed sputum induction to have a higher yield of culture positivity per specimen than nasopharyngeal aspiration (OR 0.69 (95% CI 0.52 to 0.91)).

Very low quality of evidence from 3 cross-sectional evaluations in 1830 specimens from children and young people with suspected pulmonary tuberculosis showed gastric aspiration/lavage to have a higher yield of culture positivity per specimen than nasopharyngeal aspiration, though the effect was not statistically significant (OR 0.68 (95% CI 0.45 to 1.04)).

Very low quality of evidence from 3 cross-sectional evaluations in 273 children and young people with suspected pulmonary tuberculosis showed gastric aspiration/lavage (3 samples) to have a yield of culture positivity per patient higher than bronchoalveolar lavage (1 sample), though the effect was not statistically significant (OR 1.41 (95% CI 0.95 to 2.1)).

Low quality evidence from 1 study randomised controlled trial in 36 ‘uncooperative’ children and young people with suspected pulmonary tuberculosis showed intranasal sedation to improve the acceptability of nasogastric aspiration to parents, as well as to the clinicians performing the procedure.

No evidence was identified for the incidence of adverse events or the volume of sample obtained per collection.

3.4.4.4 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 488 records were returned. On a title and abstract sift, no records matched the inclusion criteria.

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3.4.4.51 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that the test-positivity (specifically, culture-, smear- and PCR-positivity) and sample volume per collection are the most critical to decision making. With regards to test-positivity, culture-positivity was considered the most important, with the outcome reported on a per patient rather than per specimen basis. Furthermore, these are linked, with an adequate sputum sample (5 ml or more) being one of the factors that can improve the positive yield of culture or microscopy. Other factors that might improve the positive yield include the concentration of the sputum sample, the number of samples analysed and specific microbiological approach taken. Adverse events and the acceptability of the procedure from patient, carer and clinician perspectives were also considered important for decision-making, though these outcomes were not considered as critical. The GDG felt that the paucity of data for these outcomes was noteworthy, and further data on this would have been useful. No data was identified for the number of collection events required to make a diagnosis, nor the time to diagnosis or treatment initiation, which the GDG also felt may have assisted their decision-making.
Trade-off between benefits and harms	In the UK, sputum induction and nasogastric aspiration, with or without lavage, are the most commonly used approaches to collecting respiratory samples from children unable to expectorate spontaneously. Sputum induction is simple and non-invasive, and, if successful, often precludes the need for more invasive techniques. The key feature of procedure is the inhalation of a nebulised hypertonic saline solution, which liquefies respiratory secretions and promotes coughing, therefore allowing expectoration of a respiratory sample. Another common feature is the use of a bronchodilator, such as salbutamol, for the relief of bronchospasm, which can be very worrying and frightening to young children. However, since the procedure produces coughing and, consequently, can lead to the expulsion of infectious droplets into the room, infection control measures are very important. An appropriately engineered and ventilated area, such as a negative pressure room, is essential to the safe practice of this procedure.. Although referral is possible, the group emphasised that diagnosis, and therefore treatment initiation, should not be delayed: where these facilities or staffing are not readily available, gastric aspiration should be used. Gastric aspiration is the suctioning of swallowed sputum from the stomach using a nasogastric tube. In the case of gastric lavage, a saline solution is first funnelled into the stomach via the nasogastric tube. A pre-collection fast is important in ensuring that samples are not contamined with food and contain swallowed sputum only, and therefore of an adequate quality. Repeated gastric aspirations or lavages can be done without extracting the nasogastric tube between sample collections (for example, over 3 consecutive days), which can mean less distress for the child although it does require the child to be admitted. Additionally, there is the option of sedating patients during the procedure. The acceptability of this option was explored in one of the identified studies, and the GDG noted a trend across a number of measures (including views from parents and clinicians on the usefulness of the sedation and the impact on the child's and parent's outlooks) that favoured the use of sedation compared to the use of a placebo, although they seemed equally good at improving the tolerability of the procedure to children. In addition to discussing how a sample should be collected, the GDG also commented on when a sample should be collected. They felt that the emphasis on early morning sample may be overemphasized, leading to delays in diagnosis. Prompt diagnosis, and consequently treatment, may be more important than waiting until an early morning sample has been obtained, especially in people with more severe disease. However, in people who are relatively "well", waiting to get good an optimal sample (that is, an early morning sample) is appropriate. This applies to people of all ages. The group also felt it important to encourage more routine specimen collection. In practice, clinicians sometimes rely solely on chest x-rays to start treatment, but with the expanding problems of drug resistance practice should move more towards microbiological diagnosis. Furthermore, although this may not always be

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	key in clinical management, specimens can be very useful to public health efforts.
Trade-off between net health benefits and resource use	In addition to the need for an appropriately engineered and ventilated area, such as a negative pressure room, for the safe practice of sputum induction (see above), another resource implication is the requirement for a physiotherapist (or other adequately trained healthcare professional). It can be difficult to ensure a physiotherapist for the collection of all 3 specimens, though the group still felt that the recommendation was justified. The group noted that these requirements represent significant resource considerations and may not be feasible in smaller hospitals or health centres.
Quality of evidence	The GDG noted that no evidence was identified for transbroncheal biopsy, and only limited evidence was available for bronchoalveolar lavage, laryngeal swab and lung puncture aspiration. Furthermore, there was a paucity of evidence for outcomes other than test positivity; the GDG found the lack of data on acceptability and adverse effects to be particularly notable. The overall quality of the data for each outcome varied from low to very low. In intervention reviews GRADE would ordinarily take 'low quality' to be the starting point for outcome data obtained from cross-sectional studies. However, it was felt that for the proportion of specimens to give a positive test result, cross-sectional data using paired specimens could arguably be the most appropriate. Therefore, the reviewer modified the quality assessment for test positivity such that the starting point for cross-sectional data was 'moderate quality'. Despite this, all outcomes obtained from the cross-sectional studies remained 'very low quality'. Poor reporting were common in the identified evidence, including failure to describe methods for the selection and enrolment of patients, the use of blinding, outcome definitions, including the thresholds used for test positivity, and reasons for exclusions or missing data. In one study (Jiménez et al, 2013), which examine the use of gastric lavage and sputum induction, the reported reasons for exclusion were inappropriate, with data for participants positive for nontuberculous mycobacteria not included in the study report. Furthermore, inadequate sample sizes were common, and many estimates of effect were therefore imprecise.
Other considerations	Most studies specify 'experienced personnel' in the performance of the sample collection. The GDG noted that this might be challenging to roll out more routinely. The evidence comparing sputum induction and gastric aspiration could not distinguish between the two with regards to test positivity. If 2 specimens were used, gastric aspiration was favoured; if 3 specimens were used, culture favoured sputum induction, where as microscopy and PCR favoured sputum induction, though without achieving significance. In this way, the GDG noted that over multiple specimens, the estimates for test positivity converge. The group also noted that a single study (Mukherjee et al, 2013) was driving any overall preference in favour of gastric aspiration over sputum induction; none of the other included studies were as clear-cut. Overall, its difficult to say which is better in terms of effectiveness, though the evidence doesn't seem to support the previous guidance (CG117) in favouring sputum induction. In terms of feasibility and resource use, as well as the group's own experience with regards to the invasiveness of the procedure and distress experienced by the child, gastric aspiration seems to be preferable. The GDG felt that there was insufficient evidence to suggest that other procedures should be used in place of sputum induction or gastric aspiration. In the case of nasopharyngeal aspiration, this was because of the evidence of lower yields of test positivity for this procedure In the case of bronchoalveolar lavage, laryngeal swab and lung puncture aspiration, the GDG considered the paucity of evidence and the invasiveness of these procedures, each of which necessitate highly skilled personnel and significant sedation and analgesia. The use of general anaesthesia reduces the distress of the child involved but carries inherent risks, whereas intramuscular injections of local anaesthesia can be very painful and upsetting for the child, as well as their parents or carers and the clinician administering the intervention. Because of the invasive nature of all of the available techniques to one degree or another, the GDG felt it was important to emphasise that these procedures should

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	only be used in patient in whom parenchymal (as opposed to, for example, lymph node) disease is suspected based on radiological findings (and appropriate TST and/or IGRA responses) as this is the only disease type for which the specimens collected will be relevant. In considering the subgroup of patients who are less than 5 years of age, the group noted the same hierarchy or approaches as in the overall review, although sputum induction now appears to dominate gastric aspiration. Despite this, they did not feel that there was sufficient evidence to make a specific recommendation for the use of sputum induction over gastric aspiration in this age group, particularly since the estimates of effect did not achieve significance.

3.4.5 Recommendations

See section 3.3.7

3.5 Diagnosing active pulmonary tuberculosis: methods for smear and culture – position statement

3.5.1 Clinical introduction

This section aims to establish the most effective methods for obtaining an accurate diagnosis of active pulmonary tuberculosis by sputum smear microscopy and culture. These are key components of the diagnostic pathway, and procedures for which a number of possible approaches or variations in practice exist. In addition to achieving more accurate diagnostic information, standardisation of these processes helps to assure the equivalence of investigation strategies in different laboratories and is essential for public health surveillance, research and development activities.

3.5.2 Review question

What are the most effective methods for i) sputum smear microscopy and ii) sputum culture in establishing an accurate diagnosis of active pulmonary TB?

3.5.3 Position statement

Although a review was initially considered, the GDG felt that the UK Standards for Microbiology Investigations (SMIs) for examination of the Mycobacterium species (B40 Investigation of specimens for mycobacterium species) available from Public Health England, were the most appropriate resource for answering this question.

3.5.4 Evidence to recommendations

Relative value of different outcomes	Not applicable.
Trade-off between benefits and harms	Although a review was initially considered, the GDG felt that the UK Standards for Microbiology Investigations (SMIs) for examination of the Mycobacterium Tuberculosis complex, available from Public Health England, were the most appropriate resource for answering this question. SMIs comprise an evidence-based collection of recommended algorithms and procedures covering all stages of the investigative process in microbiology. They establish a good standard of practice to which all clinical and public health microbiology laboratories in the UK are expected to work. In addition to being evidence-based and NICE-accredited, these SMIs are more comprehensive than the reviews initially proposed here, and

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	duplication of the development work was not considered necessary.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	The GDG felt that the SMIs were of sufficient quality to guide practice in this area, given that they are both comprehensive and NICE-accredited.
Other considerations	None.

3.5.5 Recommendations

None

3.6 Diagnosing active extrapulmonary tuberculosis: clinical signs, symptoms or risk factors – position statement

3.6.1 Clinical introduction

Tuberculosis can affect nearly every extrapulmonary site, sometimes with a combination of pulmonary and extrapulmonary sites, or single or multiple extrapulmonary sites.

Much in the clinical decision-making process depends on making an assessment of:

- the likelihood of exposure (depending on country of birth, ethnicity, time in prison, homelessness, health care worker, family or household contact), and
- the likelihood that infection has progressed to disease or could progress quickly (for example, HIV positive status or other evidence of being immunocompromised).

Some sort of radiological imaging is required for almost all cases in order to:

- identify the site of pathology,
- assess the extent of the disease, and
- guide tissue or fluid sampling for microbiological and histological analysis.

A chest x-ray (or possibly a CT scan) is also needed to assess the risk of infectiousness – that is, does the patient in fact have both extrapulmonary and pulmonary tuberculosis.

3.6.2 Review question

What clinical signs, symptoms or risk factors are suggestive of a diagnosis of active extrapulmonary TB?

3.6.3 Position paper

3.6.3.1 Introduction

Although a review was initially considered, the GDG felt that there would be limited evidence of sufficient quality to answer this question, and that knowledge on the topic was already well established. Therefore, it was decided that drafting a position paper on the current state of practice in the UK would be the most appropriate resource for answering this question.

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3.6.3.21 Question(s)

For each of the sites listed below, produce/consider the following:

- a bulleted list detailing the signs and symptoms you have found most effective in practice and why
- what are the key things you consider, what's your decision making process?
- are there any differences for key subgroups, including children and young people and people with HIV?
- are there any areas of uncertainty?

Sites:

- pleural tuberculosis
- CNS tuberculosis
- spinal tuberculosis
- bone and joint
- genitourinary tuberculosis
- gastrointestinal tuberculosis
- lymph node tuberculosis
- pericardial tuberculosis
- disseminated, including miliary, tuberculosis
- other sites of disease

3.6.3.30 Authors

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3.6.3.45 Position

The signs and symptoms of active extrapulmonary tuberculosis can broadly be divided into 2 groups:

- the generalised, systemic chronic inflammatory process of tuberculosis (core signs and symptoms), and
- the specific localising signs and symptoms that may give a guide to the main site of disease.

Core signs and symptoms

For all extrapulmonary presentations of tuberculosis there is a highly variable combination of core, often vague or non-specific signs and symptoms which patients may present with, or which healthcare professionals may ask about. Asking is important because a fairly consistent (though not invariable) feature of tuberculosis is that the onset of symptoms is slow and gradual over a number of weeks or months. Patients often find it difficult to pinpoint when illness began, and often do not pay attention to all symptoms.

Core symptoms include chronic fever (feeling hot or cold in waves), night sweats, weight loss, general malaise and fatigue (all indicators of the underlying chronic inflammatory process), generally for a period of at least 2 weeks.

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Core signs include recorded fevers and cachexia (a wasting syndrome marked by weight loss, muscle atrophy, fatigue, weakness, and significant loss of appetite).

Site-specific signs and symptoms

On top of these core signs and symptoms there may be additional symptoms and signs for each specific form of extrapulmonary tuberculosis:

Pleural tuberculosis

Pleural tuberculosis makes up 8.6% of tuberculosis cases in the UK[v].

Signs include unilateral pleural effusion (dullness to percussion, reduced breath sounds, reduced transmitted sounds). Sometimes the effusion is too small to be detected clinically and so there are no localising clinical signs at all. In these cases; effusion is detected radiologically by x-ray, CT or MRI.

Symptoms include chest pain and shortness of breath, particularly if the pleural effusion is large.

It should be noted that effusion may resolve apparently spontaneously, which may deter clinicians from considering a diagnosis of pleural tuberculosis. Diagnostic efforts should still be undertaken, and treatment appropriate for those with active tuberculosis should still be considered.

Central nervous system tuberculosis

Although only forming 4.5% of tuberculosis in the UK[w], tuberculosis of the central nervous system is of disproportionate importance because of the significant morbidity and mortality associated with it.

Symptoms include variable combinations of one or more of the following: headache, vomiting, confusion, a decreased level of consciousness, behaviour changes, mood changes or seizures, each gradually increasing in severity or frequency.

Signs include variable combinations of one or more of the following: meningism (which can manifest as neck stiffness or photophobia), hydrocephalus, central neurological deficit (any pattern is possible, but classically oculomotor nerve palsy as part of the predominantly basal meningitis, as well as cranial nerve palsy and hemiplegia). Sometimes there are no localising clinical signs, and evidence of pathology is only clear on radiological imaging (x-ray, CT or MRI) or examination of the cerebrospinal fluid. A chest x-ray shows evidence of pulmonary disease in a high proportion of cases.

Spinal tuberculosis

Spinal tuberculosis, specifically that affecting the bone, forms 4.5% of tuberculosis in the UK[x].

Symptoms include chronic (that is, for more than 3 weeks) bone pain and/or swelling and/or warmth of bones of a limb.

Signs include localised spinal tenderness, neurological deficit (depending on level of lesion(s) and extent and nature of spinal cord involvement (paraparesis or paraplegia are possible)) and spinal deformity. Sometimes there are no localising clinical signs, and evidence of pathology is only clear on radiological imaging (x-ray, CT or MRI). Conversely,

[v] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London
[w] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London
[x] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London

given that almost 50% of cases in some series have multifocal spinal involvement, there may be signs at more than just the apparent site of the problem; in this case, radiological examination of the whole of the spinal cord is indicated.

Bone and joint tuberculosis

Bone and joint tuberculosis outside of the spine is rare, accounting for just 0.5% of tuberculosis cases in the UK[y].

Symptoms include localised pain in the affected bone or joint. Often only one bone or joint is affected in each patient.

Signs include a combination of localised joint or bone tenderness, swelling or deformity, along with reduced limb or joint functionality. Sometimes there are no localising clinical signs, and evidence of pathology is only clear on radiological imaging (x-ray, CT or MRI).

Genitourinary tuberculosis

Genitourinary tuberculosis accounts for 2.2% of tuberculosis in the UK[z]. It is a rare presentation in children.

Symptoms include loin pain (if there is renal involvement), recurrent bacterial infections (if upper or lower renal tract obstruction). Women may experience pelvic pain, dysuria, haematuria and/or dyspareunia. Men may experience variable combinations of testicular swelling and/or pain, dysuria and/or haematuria. Infertility may also occur, and sometimes there are no localising clinical symptoms at all.

Signs include loin or lower abdominal tenderness. Haematuria or pyuria occasionally. Sometimes there are no localising clinical signs, and evidence of pathology is only clear on radiological imaging (abdominal ultrasound, CT or MRI).

Gastrointestinal tuberculosis

Gastrointestinal tuberculosis accounts for 5.5% of tuberculosis in the UK[aa].

Symptoms include variable combinations of abdominal pain, anorexia, nausea, vomiting, as well as disturbance of bowel habit, including intermittent diarrhoea or constipation.

Signs include abdominal tenderness, sometimes abdominal masses (omental, nodes, or localised bowel inflammation), signs of small bowel obstruction, and abdominal distention on examination. Sometimes there are no localising clinical signs, and evidence of pathology is only clear on radiological imaging (abdominal ultrasound, CT or MRI).

Lymph node tuberculosis

Approximately a third of all tuberculosis in the UK occurs in lymph nodes[bb].

Symptoms include lymph node enlargement – most commonly in the neck, and usually painless. Sometimes there is abscess formation and discharge of pus from necrotic nodes, often with minimal apparent systemic disturbance.

Signs include palpable chain(s) of matted nodes, sometimes with abscess and sinus formation and discharge of pus.

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[y] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London
[z] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London
[aa] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London
[bb] Public Health England (2014) Tuberculosis in the UK 2014 report. Public Health England: London

Pericardial tuberculosis

Pericardial tuberculosis is a rare presentation in the UK.

Symptoms are often non-specific, but may include shortness of breath, reduced exercise tolerance or tachycardia.

Signs include pericardial effusion – associated with an indistinct apex beat, muffled heart sounds, pulsus paradoxus, signs of right-sided heart failure (raised jugular venous pressure, tender hepatomegaly, peripheral dependent oedema) – or pericardial constriction (mainly right-sided heart failure). Sometimes signs are subtle and imaging (such as echocardiography) may be required.

Disseminated, including miliary, tuberculosis

Disseminated, including miliary, tuberculosis is a rare presentation in the UK.

Generally patients experience only core signs and symptoms. Core signs include recorded fevers and cachexia (that is, a wasting syndrome marked by weight loss, muscle atrophy, fatigue, weakness, and significant loss of appetite). Core symptoms include chronic fever (feeling hot or cold in waves), night sweats, weight loss, general malaise and fatigue (all indicators of the underlying chronic inflammatory process), generally for a period of 2 weeks or more. It is very rare to have any localising signs or symptoms.

Ocular tuberculosis

Again, ocular tuberculosis is a rare presentation in the UK.

Symptoms include chorio-retinitis, phlyctenular conjunctivitis.

Tuberculosis of the skin

Tuberculosis of the skin is also a rare presentation in the UK.

Symptoms include lupus vulgaris, tuberculids, erythema nodosum. Most manifestations include painless chronic thickening and discolouration of the skin, sometimes with local abscess formation and deep extension to underlying tissues. These are evident on examination.

Key subgroups: children and young people, and people with HIV

For both of these subgroups (HIV-positive and children), the disease process is taking place on the background of a blunted immune response. This is dependent on the degree of immuncompromise (more severe in very young children or patients with low CD4 counts). However, in general, the more immunocompromised, the faster the disease progression (less gradual in onset) and the greater the chance of disease at more than one site.

3.6.4 Evidence to recommendations

Relative value of different outcomes	Not applicable.
Trade-off between benefits and harms	The GDG discussed the position paper drafted on the clinical signs, symptoms or risk factors for active extrapulmonary tuberculosis. Although they felt it was informative, they did not feel it was sufficient grounds on which to produce recommendations.
Trade-off between net health benefits	Not applicable.

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and resource use	
Quality of evidence	The GDG noted the consensus status of this position paper and agreed quality of evidence was very low
Other considerations	None.

3.6.5 Recommendations

1

2 None.

3.7 Diagnosing active extrapulmonary tuberculosis: tests

3.7.1 Clinical introduction

Most forms of extrapulmonary tuberculosis have a lower bacterial load than for pulmonary disease, being so-called paucibacillary forms. A relatively low proportion of cases have positive microscopy for acid-fast bacilli, and with the lower bacterial loads it takes longer to obtain positive cultures.

With many of the extrapulmonary sites,results from biopsy histology, or, in the case of lymph node disease, needle aspiration cytology, is available well before culture. The finding of caseating granulomas, or granulomas with Langhan's giant cells on histology or cytology, is very highly suggestive of tuberculosis. A number of other conditions however can cause non-caseating granuloma formation.

The yield of histology/cytology depends on tissue sample size, which is much smaller with aspiration cytology than biopsy, and on the level of immune response which generates the histological appearances. In HIV-positive individuals the histological response depends on the level of immunosuppression. With levels of CD4 lymphocytes above 200/µl typical TB histology is the rule, but as the CD4 cell count falls, particularly below 100/µl, less and less granuloma formation occurs, and with profound immunosuppression there may be no cellular histological response at all. In these circumstances however there is an increased likelihood of acid-fast bacilli being seen microscopically.

A similar diagnostic problem can occur when patients with a very low CD4 count are started on highly active antiretroviral therapy. The rapid fall in HIV viral load and rise in CD4 count allows an immune response to be mounted to either of these organisms, which was not previously possible. Enlargement of cervical and intra-abdominal lymph nodes in particular are described in this context, which is known as the immune reconstitution syndrome (IRIS).

In some cases of extrapulmonary tuberculosis, particularly in those presenting to surgeons, the diagnosis of tuberculosis is not considered likely in the differential diagnosis, and the doctor does not send any material for culture, instead placing the entire sample in formalin. This then completely precludes any attempt at bacterial culture, although if acid-fast bacilli are seen histologically it still allows NAAT-based techniques to be used.

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3.7.2 Review question

Apart from culture, what other tests are effective in establishing an accurate diagnosis of active extrapulmonary tuberculosis in people with suspected active extrapulmonary tuberculosis?

In patients who are culture negative, what other tests are effective in establishing an accurate diagnosis of active extrapulmonary tuberculosis in people with suspected extrapulmonary tuberculosis?

3.7.3 Evidence review

For this review, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the diagnosis of active extrapulmonary tuberculosis. Test-and-treat RCTs, quasi-RCTs, cross-sectional studies and systematic reviews of these study designs were considered for inclusion. Case-control studies using a culture-based reference standard were considered for inclusion where none of the above study designs are available. Papers of

interest were those that compared diagnostic methods against a culture-based reference standard. (See appendix C for the full review protocol).

Trials were excluded if:

- papers for which the site of disease is non-specific
- participants did not have suspected TB;
- the reference standard was not culture-based, or not a combination of treatment response plus other clinical criteria and/or histology (test-and-treat RCTs, quasi-RCTs, systematic reviews and cross-sectional studies only);
- tests were not conducted concomitantly;
- the test was in-house rather than commercial;
- the sample size was less than 30, unless pooled in a meta-analysis;
- for diagnostic test accuracy data, studies in which a 2x2 table could not be populated;
- case studies, case series and narrative reviews.

The evidence was considered by site of disease being investigated. Specifically, the sites of disease covered were bone and joint, central nervous system, genitourinary, gastrointestinal, lymph node, pericardial, pleural and disseminated, including miliary.

From a database of 4515 abstracts, 494 full-text articles were ordered (although this included possible inclusions for suspected pulmonary disease) and 8 systematic reviews and 30 papers met the inclusion criteria. A further 3 systematic reviews and 1 paper were identified in the update searches. This represented:

- 1 systematic review and 13 studies containing 106 evaluations for pleural tuberculosis,
- 1 study containing 1 evaluation for bone and joint tuberculosis,
- 3 systematic reviews and 9 studies containing 77 evaluations for central nervous system tuberculosis,
- 1 systematic review and 2 studies containing 8 evaluations for genitourinary tuberculosis,
- 3 systematic reviews and 4 studies containing 34 evaluations for gastrointestinal tuberculosis,
- 2 systematic reviews and 11 studies containing 34 evaluations for lymph node tuberculosis, and
- 1 systematic review and 2 studies containing 9 evaluations for pericardial tuberculosis.

No studies were found that investigated the diagnosis of disseminated, including miliary, tuberculosis, or tuberculosis in other sites not specified above.

Also no evidence were found to assess the use of diagnostic test in patient who are culture negative.

Again, where possible, the reviewer used the ‘metandi’ command in STATA to meta-analyse the data into pooled effect estimates. Where STATA was not appropriate, the ‘mada’ command in R was used though this can only produce pooled estimates for sensitivity, not specificity. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

The evidence base suffered from the presence of significant heterogeneity, poor study design and reporting and a lack of generalisability to the UK context.

All recommendations were made using the recommendations made in the previous guideline (CG117) as a starting point.

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3.7.41 Evidence statements

2 Diagnosis of pleural tuberculosis

3 Low quality of evidence from 6 cross-sectional evaluations on 294 specimens from adults
4 with suspected pleural TB comparing sputum smear microscopy with a culture-based
5 reference standard showed microscopy to have a pooled sensitivity of 10.5% (95% CI 3.7 to
6 26.4%). This included 1 evaluation of fluorescence microscopy, the preferred smear
7 technique according to Public Health England's Standards for Microbiology Investigations[cc];
8 sensitivity for this technique was 0% (95% CI 0 to 84%) and specificity was 100% (95% CI 69
9 to 100%).

10 Very low quality of evidence from 26 cross-sectional evaluations on 1686 specimens from
11 adults with suspected pleural TB comparing commercial NAATs with a culture-based
12 reference standard showed commercial NAATs to have a pooled sensitivity of 53.0% (95%
13 CI 33.2 to 71.9%). Low quality evidence from the same 13 evaluations produced a pooled
14 specificity of 99.4% (95% CI 98.1 to 99.8%).

15 Low quality of evidence from 1 cross-sectional evaluation on 45 specimens from adults with
16 suspected pleural TB comparing cytology (specifically, the histopathologic examination of
17 pleural biopsy specimens fixed in formalin for caseating granuloma) with a culture-based
18 reference standard showed cytology to have a sensitivity of 53.9% (95% CI 34.7 to 73.0%).
19 Moderate quality evidence from the same evaluation produced a specificity of 97.4% (95% CI
20 90.4 to 100%).

21 Very low quality of evidence from 65 evaluations (cross-sectional and a number of possible
22 case-control) on 8222 specimens from adults with suspected pleural TB comparing
23 adenosine deaminase assays (ADAs) with a culture-based reference standard showed
24 ADAs to have a pooled sensitivity of 94.2% (95% CI 91.5 to 96.0%) and a pooled specificity
25 of 91.3% (95% CI 89.1 to 93.1%).

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26 Diagnosis of central nervous system tuberculosis

27 Low quality of evidence from 6 cross-sectional evaluations on 706 specimens from adults
28 with suspected TB meningitis comparing sputum smear microscopy with a culture-based
29 reference standard showed microscopy to have a pooled sensitivity of 68.8% (95% CI 32.7 to
30 90.9%).

31 Very low quality of evidence from 29 cross-sectional evaluations on 2810 specimens from
32 adults with suspected TB meningitis comparing commercial NAATs with a culture-based
33 reference standard showed commercial NAATs to have a pooled sensitivity of 70.6% (95%
34 CI 53.3 to 83.5%).

35 Very low quality of evidence from 13 cross-sectional evaluations on 1092 specimens from
36 adults with suspected TB meningitis comparing ADAs with a culture-based reference
37 standard showed ADAs with a threshold for test positivity of 4 U/l to have a pooled sensitivity
38 of 92.7% (95% CI 89.1 to 95.4%) and a pooled specificity of 72.3% (95% CI 69.0 to 75.4%).
39 ADAs with a threshold for test positivity of 8 U/l had a pooled sensitivity of 63.0% (95% CI
40 57.1 to 68.6%) and a pooled specificity of 84.8% (95% CI 82.1 to 87.3%), and a pooled
41 sensitivity of 49.5% (95% CI 43.6 to 55.4%) and a pooled specificity of 90.7% (95% CI 88.5
42 to 92.7%) when the threshold was set at 10 U/l.

[cc] Public Health England (2014) UK Standards for Microbiology Investigations: B40 Investigation of Specimens for Mycobacterium species. Public Health England: London

Diagnosis of gastrointestinal tuberculosis

Very low quality of evidence from 3 cross-sectional evaluations on 124 specimens from adults with suspected gastrointestinal tuberculosis comparing sputum smear microscopy with a culture-based reference standard showed microscopy to have a pooled sensitivity of 42.4% (95% CI 12.2 to 79.6%).

Very low quality of evidence from 14 cross-sectional evaluations on 965 specimens from adults with suspected gastrointestinal tuberculosis comparing IGRAs with a culture-based reference standard showed IGRAs to have a pooled sensitivity of 89.7% (95% CI 82.6 to 94.1%) and a pooled specificity of 93.3% (95% CI 82.9 to 97.6%).

Very low quality of evidence from 17 cross-sectional evaluations on 1617 specimens from adults with suspected gastrointestinal tuberculosis comparing ADAs with a culture-based reference standard showed ADAs to have a pooled sensitivity of 94.9% (95% CI 89.7 to 97.5%) and a pooled specificity of 96.2% (95% CI 93.9 to 97.7%).

Diagnosis of genitourinary tuberculosis

Low quality of evidence from 2 cross-sectional evaluations on 72 specimens from adults with suspected genitourinary tuberculosis comparing sputum smear microscopy with a culture-based reference standard showed microscopy to have a pooled sensitivity of 36.3% (95% CI 19.2 to 57.8%).

Moderate quality of evidence from 1 cross-sectional evaluation on 42 specimens from adults with suspected genitourinary tuberculosis comparing radiology (specifically, renal calcification, caliceal destruction, infundibular stenosis, cavitation, ureteral stricture, vesicoureteral reflux and small capacity bladder) with a culture-based reference standard showed radiology to have a sensitivity of 91.4% (95% CI 82.2 to 100%). Low quality evidence from the same evaluation produced a specificity of 28.6% (95% CI 0.0 to 62.0%).

Low quality of evidence from 4 cross-sectional evaluations on 208 specimens from adults with suspected genitourinary tuberculosis comparing commercial NAATs with a culture-based reference standard showed commercial NAATs to have a pooled sensitivity of 56.9% (95% CI 0.0 34.9 to 76.4%).

Low quality of evidence from 1 cross-sectional evaluation on 30 specimens from adults with suspected genitourinary tuberculosis comparing IGRAs with a culture-based reference standard showed IGRAs to have a sensitivity of 91.7% (95% CI 76.0 to 100%) and a specificity of 88.9% (95% CI 74.4 to 100%).

Diagnosis of lymph node tuberculosis

Low quality of evidence from 7 cross-sectional evaluations on 799 specimens from adults with suspected lymph node tuberculosis comparing sputum smear microscopy with a culture-based reference standard showed microscopy to have a pooled sensitivity of 36.4% (95% CI 27.5 to 46.5%) and a pooled specificity of 94.4% (95% CI 78.4 to 98.8%).

High quality of evidence from 1 cross-sectional evaluation on 250 specimens from adults with suspected lymph node tuberculosis comparing cytology (specifically, the cytological criteria for diagnosis of tuberculous lymphadenitis were defined as epithelioid cell granulomas with or without multinucleate giant cells and caseation necrosis) with a culture-based reference standard showed cytology to have a sensitivity of 99.2% (95% CI 97.7 to 100%). Moderate quality evidence from the same evaluation reported a specificity of 49.2% (95% CI 40.2 to 58.1%).

Very low quality of evidence from 26 cross-sectional evaluations on 1824 specimens from adults with suspected lymph node tuberculosis comparing commercial NAATs with a culture-

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based reference standard showed commercial NAATs to have a pooled sensitivity of 86.5% (95% CI 78.5 to 91.8%) and a pooled specificity of 92.4% (95% CI 88.7 to 95.0%).

Diagnosis of pericardial tuberculosis

Very low quality of evidence from 2 cross-sectional evaluations on 115 specimens from adults with suspected pericardial tuberculosis comparing commercial NAATs with a culture-based reference standard showed commercial NAATs to have a pooled sensitivity of 51.5% (95% CI 13.8 to 87.6%).

Very low quality of evidence from 5 cross-sectional evaluations on 421 specimens from adults with suspected pericardial tuberculosis comparing ADAs with a culture-based reference standard showed ADAs to have a pooled sensitivity of 88% (95% CI 82 to 91%). Low quality evidence from the same evaluations reported a pooled specificity of 83% (95% CI 78 to 88%).

Diagnosis of disseminated, including miliary, tuberculosis

No studies were found that investigated the diagnosis of disseminated, including miliary, tuberculosis.

Diagnosis of tuberculosis in other sites

No studies were found that investigated the diagnosis of tuberculosis in other sites not specified above.

Diagnosis in patients who are culture negative

No studies were identified.

3.7.5 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 2263 records were returned. After a title and abstract sift, no records were found to match the inclusion criteria.

3.7.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that diagnostic test accuracy and time to diagnosis or treatment initiation were the most critical to decision making. The GDG noted that, in practice, there is a trade-off between sensitivity and specificity for many tests. Although the GDG would prefer to recommend tests that perform well on both measures, on discussing their relative importance the group felt that sensitivity, and the capacity of highly sensitive tests to rule out disease, was more important to their decision-making. The GDG also considered the accuracy that they would consider to be 'acceptable' in a test, and specified a threshold for sensitivity of 70% and a threshold for specificity of 95%. The prognostic value of tests was also considered important for decision-making, as were the acceptability of approach to the patient or clinician and the incidence of adverse events associated with different diagnostic approaches, though these outcomes were not considered critical. Despite this, no data on these outcomes was identified in the included papers.
Trade-off between benefits and harms	Ideally, conducting a diagnostic test would precisely identify all the people with the disease, so that they can receive appropriate care, and similarly correctly identify all patients who are disease free. In other words, a diagnostic test would ideally have a high sensitivity (a small proportion of false negatives compared to true positives) and a high specificity (a small proportion of false positives compared to

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true negatives). False negatives mean that people with active disease may not receive appropriate treatment and may be at considerable risk of morbidity and mortality as the disease advances. They also mean that those with infectious disease are not identified, creating a risk from infection to those around them. Alternatively, a false positive may mean that an individual undergoes unnecessary treatment or isolation, which may both have a significant impact on that person's quality of life.

The GDG agreed that anyone with extrapulmonary tuberculosis should be checked for pulmonary TB as the route of infection is through the lungs, therefore there is a risk that there is also disease there.

Additionally, the GDG noted the generally poor performance of rapid diagnostic tests with regards to sensitivity. This high rate of false negativesraised the concern that people with active extrapuomonary disease would be started on treatment late, increasing the severity of disease and the risk of treatment failure. For this reason, negative results in any test except culture should be considered carefully, particularly for disease in sites such as the central nervous system where the consequence of misdiagnosis can be severe.

Pleural tuberculosis

The GDG noted how poorly microscopy on pleural samples performed with regards to sensitivity. However, the group did not feel that this evidence was strong enough to warrant the removal of microscopy from the diagnostic pathway for pleural tuberculosis, particularly given its prominence in standard practice, its usefulness in their own experience and its low cost.

No evidence was found explicitly investigating the diagnostic accuracy of chest x-rays for the diagnosis of pleural tuberculosis. However, in their clinical experience, the group had found chest x-rays to be a useful source of information in the diagnosis of pleural tuberculosis, and that the test should therefore remain in the diagnostic pathway.

Evidence for cytology was limited, with just 1 study investigating its use in the diagnosis of pleural tuberculosis. Although the sensitivity of cytology did not reach the agreed threshold for acceptability in this single study, the group did feel there was sufficient evidence upon which to remove cytology from the diagnostic pathway for pleural tuberculosis.

The group noted the poor sensitivity of NAATs when used on pleural specimens. They also noted the considerable between-study variability of the estimates of effect for sensitivity. They felt that this likely stemmed from the small size of many of the studies, as well as variation in the samples used – some studies used pleural fluid samples, some pleural tissue. The group noted that pleural tissue samples are generally thought to produce more accurate results. For these reasons, the GDG did not feel that there was sufficient evidence to support the addition of NAATs to the diagnostic pathway for pleural tuberculosis.

The group felt that in patients in whom there is a suspicion of pleural tuberculosis – for example, due to clinical and/or radiological criteria, such as pleural effusion on X-ray – the poor sensitivity observed for microscopy and NAATs means that additional tests should be conducted on pleural fluid and biopsy specimens.

Considerable evidence (65 evaluations) investigating the use of ADAs in the diagnosis of pleural tuberculosis was identified. Although the group noted the low quality of the evidence, as well as the between-study variation in reference standard used and the estimates of effect for both sensitivity and specificity, they also noted that when the estimates were pooled the test performed well. Although the GDG was generally unfamiliar with this test and had very little experience its the use in practice, they could not ignore the volume of evidence and the accuracy achieved by the test. They noted that most of the study's conducted the test using Giusti's method, and that practice should reflect this. They also noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability is consistently met.

The GDG did, however, note that adenosine deaminase is not a tuberculosis-specific marker, rather it is a general marker for immune reactions occurring within lymphocytes and its presence could also be suggestive of other infections. It is

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particularly important that other conditions, such as sarcoidosis, which in addition to be associated with raised adenosine deaminase levels has a similar clinical and radiological profile, be ruled out. Therefore the group were not comfortable in recommending its use in the absence of other tests, nor did they feel that its use should necessarily be routine.

No evidence was found explicitly investigating the diagnostic accuracy of TSTs or phage-based tests for the diagnosis of pleural tuberculosis.

Bone and joint tuberculosis

Only 1 study was identified, examining the use of IGRAs in 36 participants. The group did not feel they were able to amend the recommendations made within the previous guideline given this paucity of evidence.

Central nervous system tuberculosis

Again, the GDG noted how poorly microscopy performed with regards to sensitivity. However, the group did not feel that this evidence was strong enough to warrant the removal of microscopy from the diagnostic pathway for CNS tuberculosis, particularly given its prominence in standard practice, its usefulness in their own experience and its low cost.

Although very low quality, the group felt that there was sufficient evidence to recommend the use of NAATs for the diagnosis of tuberculous meningitis, for which the tests met the threshold of acceptability for both sensitivity and specificity. They noted, however, that no evidence was available for other forms of CNS tuberculosis, such as tuberculomas, and so did not feel able to make a recommendation for their use for patients in whom these forms of tuberculosis were suspected.

The group also noted that ADAs performed well in the diagnosis of tuberculous meningitis, with a threshold for test interpretation of 4 U/l achieving good sensitivity. The group felt that this test may be particularly useful, therefore in confirming negative results provided by other tests. It is particularly important to avoid false negative results in the diagnosis of CNS tuberculosis given the severe consequences of missing a diagnosis.

Limited evidence was identified for the use of IGRAs and TSTs in diagnosing CNS tuberculosis. Therefore, the group did not feel there was sufficient grounds upon which they could make a recommendation regarding their use.

No evidence was found explicitly investigating the diagnostic accuracy of radiology, cytology, phage-based tests or antibody detection assays for the diagnosis of CNS tuberculosis. Additionally, no evidence was found for the diagnosis of forms of CNS tuberculosis other than tuberculous meningitis. Recommendations for these types of CNS tuberculosis were made by consensus within the GDG, and were based upon their own knowledge and experience.

Genitourinary tuberculosis

The GDG again noted microscopy's poor performance with regards to sensitivity. However, the group did not feel that this evidence was strong enough to warrant the removal of microscopy from the diagnostic pathway for genitourinary tuberculosis, particularly given its current place in standard practice, its usefulness in their own experience and its low cost.

The group also noted the good performance of radiography, although noted that this was based on just a single, small study. Despite this limitation, the sensitivity fell well above the stated threshold for acceptability, and the group felt that the inclusion of radiography in the diagnosis of genitourinary was justified.

The group did not feel that there was sufficient evidence to recommend the use of commercial NAATs for the diagnosis of genitourinary tuberculosis. 4 studies produced a pooled sensitivity of 56.9%, and the summary estimate did not reach the threshold for acceptability.

Although they noted the high sensitivity demonstrated by IGRAs, they also noted that this came from a single study of just 30 specimens, for which the methods of collection are unclear. The group did not feel there was sufficient evidence on

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which to base a new recommendation.

No evidence was found explicitly investigating the diagnostic accuracy of cytology, TSTs, ADAs, phage-based tests or antibody detection assays for the diagnosis of genitourinary tuberculosis.

Gastrointestinal tuberculosis

The GDG noted microscopy's poor sensitivity, but, again, the group did not feel that this evidence was strong enough to warrant the removal of microscopy from the diagnostic pathway for gastrointestinal tuberculosis. This was again predicated on the current place of microscopy in standard practice, its usefulness in their own experience and its low cost.

Having considered the evidence for the use of ADAs, the GDG felt that the high pooled sensitivity 94.9% (95% CI 89.7 to 97.5%) and specificity 96.2% (95% CI 93.9 to 97.7%) was good grounds on which to recommend the use of ADAs in the diagnosis of gastrointestinal tuberculosis, although the evidence base included a number of case-control studies. The group noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability was consistently met and that practice should reflect this.

No evidence was found explicitly investigating the diagnostic accuracy of radiography, cytology, NAATs, TSTs, phage-based tests or antibody detection assays for the diagnosis of gastrointestinal tuberculosis.

Lymph node tuberculosis

Again, the GDG noted how poorly microscopy performed with regards to sensitivity. However, the group did not feel that this evidence was strong enough to warrant the removal of microscopy from the diagnostic pathway for lymph node tuberculosis, particularly given its prominence in standard practice, its usefulness in their own experience and its low cost.

Although only 1 study was identified that investigated the use of cytology in the diagnosis of lymph node tuberculosis, the test performed well with regards to sensitivity (99.2%) and did so with a narrow confidence interval (95% CI 97.7 to 100%). The GDG felt that this supported the retention of cytology in the diagnostic pathway for lymph node tuberculosis.

The group also noted how well NAATs performed, with the 16 studies identified producing a pooled sensitivity of 89.1% (95% CI 77.8 to 95.1%) and a specificity of 90.9% (95% CI 85.8 to 94.3%). For this reason they felt that NAATs would be a useful addition to the diagnostic pathway for lymph node tuberculosis.

No evidence was found explicitly investigating the diagnostic accuracy of radiography, IGRAs, TSTs, phage-based tests or antibody detection assays for the diagnosis of lymph node tuberculosis.

Pericardial tuberculosis

The GDG discussed the evidence for NAATs and felt that, although limited, they may constitute a useful addition to the diagnostic pathway for pericardial tuberculosis given the pooled sensitivity of 51.5% (95% CI 13.8 to 87.6%).

On reviewing the evidence for ADAs, the group noted that at 88% (95% CI 82 to 91%) the pooled sensitivity across the 5 studies was considerably above the threshold for acceptability. The group felt that this was sufficient justification for adding this test to the diagnostic pathway for pericardial tuberculosis as well.

No evidence was found explicitly investigating the diagnostic accuracy of microscopy, radiography, cytology, IGRAs, phage-based tests or antibody detection assays for the diagnosis of pericardial tuberculosis.

Disseminated, including miliary, tuberculosis

No evidence was found investigating the diagnosis of disseminated, including miliary, tuberculosis. The group felt that the recommendations made within the previous guideline, CG117, should remain. Although the recommendations were made by consensus, they have proved effective in the group's own clinical

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	experience and enable diagnostic exploration of all key sites. The only addition that the group felt necessary was explicitly state that, where there are site-specific suspicions of disease the investigations specified for each of those sites should be followed. **Other sites** No evidence was found investigating the diagnosis of tuberculosis in sites other than those listed above. Therefore, the group felt that the recommendations – for the diagnosis of skin and cold abscesses (localised, tuberculous abscesses at a site other than a lymph node) – made within the previous guideline, CG117, should once again remain. These too were made by consensus and have proved effective in the group's own clinical experience. One amendment considered necessary was the uncoupling of the recommendation for the diagnosis of tuberculous cold abscesses and tuberculous liver abscesses, with the liver abscesses now integrated within the recommendations for gastrointestinal tuberculosis. The only other amendment considered necessary was to produce guidance for sites of disease other than those explicitly described. Given the rare nature of these, and the lack of evidence for them, the group felt that a TB specialist should be consulted in their diagnosis.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	No data was identified for the diagnosis of skin, cold abscess and disseminated, including miliary, tuberculosis or for people who are culture negative. For those sites where evidence was identified, the quality of the evidence was variable with the majority of evidence rated as very low or low. Also the number of studies was generally limited, and there were a number of tests for which there were no data available. For example, only 1 study examining 1 test (TST) was identified for the diagnosis of bone and joint tuberculosis. Additionally, there was a paucity of data for the HIV and age subgroups, such that the GDG did not feel able to make specific recommendations for HIV-positive and HIV-negative populations, nor for adults and those aged below 18 years (children and young people). There was also limited data available from the UK; this, for reasons described above for the diagnosis of pulmonary tuberculosis, limits the generalisability of the evidence to the UK context. The identified evidence ranged from very low to high quality, although most outcomes across the sites of disease and various tests were graded low or very low. Again, as with the evidence base for pulmonary tuberculosis, errors in the design or reporting of the studies were common, including failure to describe methods (such as those for the selection and enrolment of patients), lack of blinding (or a failure to report the use or not of blinding), inadequate sample size, inadequate gold standards for clinical case definition, and – in the case of ADAs – the use of case-control designs. Sensitivity and specificity values were often calculated in different ways, either in terms of a patient-by-patient or specimen-by-specimen basis, or in terms of the reference standard used. Additionally, there was variation in the samples used – sometimes fluid or aspirate, sometimes tissue, with tissue generally considered better with regards to diagnostic accuracy, which means, again, that 'like' is not always compared with 'like'.
Other considerations	Again, although the evidence for individual tests was considered in isolation, in reality test results would not be considered in isolation but would contribute to the overall evidence on which a diagnosis is made. As for the diagnosis of pulmonary tuberculosis, the GDG noted that a diagnosis of extrapulmonary tuberculosis is built from a combination of context, symptoms, clinical signs and investigations. The diagnosis is rarely made from a single piece of evidence, and the sensitivity

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and specificity of individual tests may not reflect the strength of multiple tests or data. This can be true for all patients, but is particularly true in children and in people who are immunocompromised, such as those with HIV.

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3.7.72 Recommendations

39. Discuss the advantages and disadvantages of both biopsy and needle aspiration with the patient, with the aim of obtaining adequate material for diagnosis. [2006]

40. Do not place part or all of any of the samples in formalin (or other fixative agent) when sending for TB culture. [2006, amended 2015]

41. Think about a diagnosis of extrapulmonary TB even if rapid diagnostic tests in, for example, cerebrospinal fluid, pleural fluid or ascitic fluid are negative. [new 2015]

42. Offer all patients presenting with extrapulmonary TB a chest posterior-anterior X-ray and, if possible, culture of a spontaneously-produced respiratory sample to exclude or confirm coexisting pulmonary TB. Also, consider site-specific tests as described below to exclude or confirm additional sites of TB. [new 2015]

43. Refer to an expert for sites not listed here, including TB of the eye and other rare sites of disease. [new 2015]

Pleural TB

44. Use the site-specific investigations listed in table 2 to diagnose and assess pleural TB.

Table 2 Site-specific investigations for pleural TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)
Pleural	Posterior-anterior X-ray	3 adequate respiratory samples: • preferably spontaneously-produced, deep cough sputum samples, otherwise induced sputum or gastric lavage • preferably 1 early morning sample	Microscopy Culture Histology	–

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		Pleural fluid	Microscopy Culture Cytology	Adenosine deaminase assay

[new 2015]

Central nervous system TB

45. Use the site-specific investigations listed in table 3 to diagnose and assess central nervous system TB.

Table 3 Site-specific investigations for central nervous system TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)
Central nervous system	CT MRI	Biopsy of suspected tuberculoma	Microscopy Culture Histology	–
		Cerebrospinal fluid	Microscopy Culture Cytology	Adenosine deaminase assay
Meningeal	CT MRI	Cerebrospinal fluid	Microscopy Culture Cytology	Nucleic acid amplification test Adenosine deaminase assay

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[new 2015]

46. Offer treatment for TB meningitis if clinical signs and other laboratory findings are consistent with the diagnosis, even if a rapid diagnostic test is negative. [new 2015]

Lymph node TB

47. Use the site-specific investigations listed in table 4 to diagnose and assess lymph node TB.

Table 4 Site-specific investigations for lymph node TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)
Lymph node	Ultrasound CT MRI	Biopsy	Microscopy Culture Histology	Nucleic acid amplification test
		Aspirate	Microscopy Culture	Nucleic acid amplification

			Cytology	test

[new 2015]:

Pericardial TB

48. Use the site-specific investigations listed in table 5 to diagnose and assess pericardial TB.

Table 5 Site-specific investigations for pericardial TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)
Pericardial	Echocardiogram	Biopsy of pericardium	Microscopy Culture Histology	–
		Pericardial fluid	Microscopy Culture Cytology	Nucleic acid amplification test Adenosine deaminase assay

[new 2015]

Gastrointestinal TB

49. Use the site-specific investigations listed in table 6 to diagnose and assess gastrointestinal TB.

Table 6 Site-specific investigations for gastrointestinal TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)
Gastrointestinal	Ultrasound CT Laparoscopy	Biopsy of omentum Biopsy of bowel Biopsy of liver	Microscopy Culture Histology	–
		Ascitic fluid	Microscopy Culture Cytology	Adenosine deaminase assay

[new 2015]

Genitourinary TB

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50. Use the site-specific investigations listed in table 7 to diagnose and assess genitourinary TB.

Table 7 Site-specific investigations for genitourinary TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)
Genitourinary	Ultrasound Intravenous urography Laparoscopy	Early morning urine	Culture	–
		Biopsy from site of disease, such as endometrial curettings or renal biopsy	Microscopy Culture Histology	–

[new 2015]

Bone and joint TB

51. Use the site-specific investigations listed in table 8 to diagnose and assess bone and joint TB.

Table 8 Site-specific investigations for bone and joint TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter management)
Bone or joint TB	X-ray CT MRI	Biopsy or aspirate of paraspinal abscess Biopsy of joint Aspiration of joint fluid	Culture	–

[new 2015]

Disseminated TB

52. Use the site-specific investigations listed in table 9 to diagnose and assess disseminated TB.

Table 9 Site-specific investigations for disseminated TB

Suspected site of disease	Imaging	Specimen	Routine test	Additional test (if it would alter

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				management)
Disseminated	CT of the thorax and head MRI Ultrasound of the abdomen	Biopsy of site of disease, including lung, liver and bone marrow	Microscopy Culture Histology	Additional tests appropriate to site
		Aspirate bone marrow Bronchial wash Cerebrospinal fluid	Microscopy (if sample available) Culture Cytology	
		Blood	Culture	

[new 2015]

Skin TB

53. Use the site-specific investigations listed in table 10 to diagnose and assess skin TB.

Table 10: Site-specific investigations for skin TB

Suspected site of disease	**Imaging**	**Specimen**	**Routine test**	**Additional test (if it would alter management)**
Skin	-	Biopsy	Microscopy Culture Histology	-

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[2015]

Localised tuberculous abscess

54. Use the site-specific investigations listed in table 11 to diagnose and assess TB in a localised, tuberculous abscess at a site other than a lymph node.

Table 11: Site-specific investigations for localised tuberculous abscess

Suspected site of disease	**Imaging**	**Specimen**	**Routine test**	**Additional test (if it would alter management)**
Abscess outside of the lymph nodes	Ultrasound or other appropriate imaging	Aspirate	Microscopy Culture Cytology	–
		Biopsy	Microscopy Culture Histology	–

[2015]

3.7.8 Research recommendations

See section 3.3.8

4 Management of active tuberculosis

4.1 Combination medicines in people with active tuberculosis [2011]

4.1.1 Clinical introduction [2011]

Adherence with drug treatment is a major determinant of the outcome of treatment. As an aid to adherence, combination tablets of three drugs (rifampicin, isoniazid and pyrazinamide) are available for use in the two-month initial phase of treatment, and of two drugs (rifampicin and isoniazid) in the four-month continuation phase of treatment. The other potential advantage of combination tablets is that they prevent accidental or inadvertent single drug therapy which can lead to acquired drug resistance within weeks in active tuberculosis disease. Care, however, is needed in the prescribing and dispensing of antituberculosis drugs in the UK, because of the similarities in names between several of the drugs (see table 17).

Table 17: **Commonly confused generic and brand names**

Drug(s)	Brand name
Rifampicin (called rifampin in USA)	Rimactane, Rifadin
Rifabutin	Mycobutin
Rifampicin + isoniazid	Rifinah, Rimactazid
Rifampicin + isoniazid + pyrazinamide	Rifater
Isoniazid	Rimifon (not marketed in UK)
Ibuprofen	Rimafen

4.1.2 Methodological introduction [2011]

Six RCTs compared fixed dose combination tablets with single-drug formulation regimens. All of the studies except one used a fixed dose combination tablet containing isoniazid, rifampicin and pyrazinamide. The exception was an Indonesian study, which compared a four-drug, fixed-dose regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol with single-drug formulations.

Four of the studies were excluded due to methodological limitations.

Two studies were included, one preliminary study from Indonesia and one study from China, which followed patients up for two years to assess relapse. In both of these studies treatment was directly observed in all patients.

4.1.3 Evidence statements [2011]

An Indonesian study compared a four-drug, fixed-dose combination (isoniazid, rifampin, pyrazinamide and ethambutol) with the same drugs in separate formulations and found there was no significant difference in terms of sputum conversion at two months or cure, failure or defaulter rates. The difference in frequency of complaints during the intensive phase between the separate and combined drugs groups was significant in terms of gastrointestinal complaints (56% *vs*. 41%, respectively, p<0.01) and muscle joint complaints (46% *vs*. 32%, respectively, p=0.01). (**1+**)

In a comparison in China of a six-month, three-drug, fixed-dose combination tablets (isoniazid, rifampin, pyrazinamide) regimen with the same drugs in separate formulations, at the end of two and six months of treatment, the bacteriological status of patients did not differ significantly in the two treatment groups as determined by examination of both sputum smear

and culture. Bacterial relapse in those who completed treatment at two years was not significantly different between the two groups. 11.8% of patients in the combined drug group, and 15.5% of patients in the separate drugs group, experienced adverse reactions, most of which were insignificant and temporary. Patients in the combined drug group actually took 99.9% of their treatment doses whilst in the separate drug group, 97% of doses were taken. (**1+**)

4.1.4 From evidence to recommendations [2011]

The increasing rates of isoniazid resistance seen in the epidemiology of England and Wales led the GDG to recommend a standard six-month, four-drug initial treatment regimen. Two studies have looked into the effect of this regimen in clinical settings in the UK and shown it to be effective and safe across susceptible and isoniazid-resistant strains.

The cost to the patient of prescription charges is lower for combination tablets.

Few studies in the evidence base for combination medicines are free from methodological limitations. Only one study used the three-drug combination available in the UK. Virtually all the data are from adult patients not known to be HIV positive, but the GDG felt that the conclusions can be extrapolated to children and HIV-positive individuals.

Given the benefits of combination tablets, and the key aim of treatment completion and adherence, the GDG recommended them.

4.1.5 Recommendations

55. Use fixed-dose combination tablets as part of any TB treatment regimen. [2006]

4.2 Dosing schedule in children and young people with active tuberculosis

4.2.1 Clinical introduction

This evidence review focused on the use of different frequencies of dosing in the chemotherapeutic treatment of active tuberculosis in children and young people. Dosing schedules can be broadly grouped into three categories:

daily dosing: patients receive their antituberculosis chemotherapy on a daily basis

intermittent dosing: patients receive their antituberculosis chemotherapy on an intermittent basis; that is, two- or three-times weekly

combination dosing: patients receive their antituberculosis chemotherapy primarily on a daily basis and then on an intermittent basis, or vice versa.

4.2.2 Review question

In children and young people with active tuberculosis, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?

4.2.3 Evidence review

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the administration of chemotherapeutic treatment for active TB in children and young people.

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Only controlled trials were considered for inclusion, first at the randomised and quasi-randomised levels, and subsequently at the non-randomised level due to the paucity of evidence in this area. Papers of interest were those that compared one dosing schedule with another in children with drug susceptible, active TB at any site of the body. (See Appendix C for the full review protocol).

Trials were excluded if:

the population included adults (aged 18 years or more);

the population included people with latent TB or drug resistant TB;

the paper focused primarily on populations with comorbidities or coexisting conditions (other than HIV) that will affect the choice or management of treatment;

the intervention included drugs not licensed in the UK; or

observational studies, case series, case studies, and narrative reviews.

From a database of 1381 abstracts, 59 full-text articles were ordered and 5 papers describing 4 primary studies met the inclusion criteria (Kansoy et al, 1998; Kumar et al, 1990; Ramachandran et al, 1998; Swaminathan et al, 2005; Te Water Naude et al, 2000). Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used Review Manager to meta-analyse the data into pooled effect estimates. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

4.2.4 Evidence statements

Very low quality evidence from 4 randomised controlled trials with over 400 patients was inconclusive about which dosing schedule was the most effective in terms of

reducing morbidity and mortality in children with active TB;

improving response to treatment as measure by disease resolution, radio,logic improvement, time to clinical response;

improving relapse rates;

improving adherence;

reducing adverse events including hepato-toxicity.

4.2.5 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 330 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

4.2.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), relapse and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. There was some debate over whether mortality, a rare but severe outcome, was more important than cure. From a patient perspective, mortality is likely to be the most important outcome, whereas cure is more clinically useful in guiding decisions regarding treatment options. Changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or

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	changes in the signs and symptoms of TB.
Trade-off between benefits and harms	Frequency of dosing is critical as daily doses of antituberculosis medications include 'pill burden' while intermittent dosages implies that higher dosages are taken less frequently. Prescription errors may result in excess doses leading to an increased risk of adverse events such as hepato-toxicity while reduced dosages may help build up drug resistance. Furthermore, just 2 or 3 missed doses can equate to a whole week of medication missed in the course of a intermittent dosing schedule. Whilst being easier to supervise twice- or thrice- weekly treatment, the large number of different pills (necessarily given as separate formulations), particularly in the initial four- drug phase, can cause nausea and adversely affect adherence. Vomiting as a side effect of rifampicin can be reduced at dosages of 600 mg or more by being taken after breakfast. Flu-like syndromes are more common with intermittent as opposed to daily rifampicin treatment. The evidence comparing dosing schedules of different frequency in children with active tuberculosis was inconclusive. The GDG noted that the incidence of mortality, relapse and adverse events seem quite low across all the studies. Whilst this is generally an encouraging pattern, it also meant that there were rarely significant estimates of effect for these outcomes and it was consequently difficult to draw conclusions about the risks of each dosing schedule. In considering an Indian RCT that compared daily and twice-weekly followed by thrice-weekly dosing, the GDG noted that more patients in the daily group had a normal chest radiograph at treatment completion than in the intermittent group, and fewer patients had residual lesions at treatment completion. However, the group did not feel confident in attributing these differences in the estimates of effect to the different dosing schedules as there were a number of other potentially confounding factors, including the presence of more cavities in the intermittent group at baseline, a sign that the group may have had more severe disease than the daily group at treatment initiation, as well as a longer duration of treatment (9 months vs 6 months) in the daily group. Furthermore, after 60 months of follow-up the direction of effect was reversed, with more patients in the intermittent group having a normal chest radiograph and more patients in the daily group having residual lesions. The GDG discussed which time point would be most useful in guiding their decision-making, and felt that the data from treatment completion was the most useful in determining which patients were no longer infectious to others, but that 60 months was generally more useful in judging the overall effectiveness of an intervention. Despite this, the presence of the aforementioned confounding factors meant that the group were not sufficiently confident in the estimates of effect at either time point, and did not feel that they could use the evidence from this RCT to make a recommendation on dosing schedules in children. The GDG thought that the greater weight gain in the daily group in the South African RCT may be noteworthy as 0.25 kg in a young child is a clinically significant difference (statistical significance could not be calculated as the authors provided only a median and an interquartile range for each group). The GDG was sceptical of adherence levels amongst the daily group in the South African RCT, particularly given that it was measured by pill counting in an unsupervised regimen. Given the lack of conclusive evidence, the GDG discussed current practice and their experiences of different dosing schedules, as well as the practicalities, advantages and disadvantages of each. The GDG noted that the use of daily dosing is the 'default' state. Additionally, they emphasised that, in their clinical experience, daily dosing is effective and that, all other things being equal, it is more effective than intermittent dosing. They felt that a strong reason to recommend intermittent dosing would be needed if they were to change the default position; that is, good evidence that intermittent dosing is effective and does not harm would be necessary. Although the evidence did not suggest that intermittent dosing schedules are less effective or more harmful than daily dosing schedules, it did not meet these

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	criteria for superiority. The group also noted that in making decisions regarding dosing schedules there is a difficult balance to strike between a more 'paternalistic' desire for curing a young patient, which tends to lean towards a daily dosing schedule, and trying to limit the discomfort inherent to all antituberculosis regimens but which are felt to be particularly common in a daily dosing schedule. Furthermore, the question of dosing schedules is not simply one of frequency, but also has strong links to issues of adherence and the delivery of Directly-Observed Therapy (DOT). The GDG noted that intermittent regimens were generally conducted using DOT in the evidence, and that they would feel uncomfortable unpicking this association in the recommendations. Additionally, the GDG felt that one of the main reasons for considering the use of intermittent dosing schedules is as a practical approach to delivering treatment through DOT. The group noted DOT can be particularly difficult and time-consuming in children, and TB services rarely have the capacity to deliver DOT on a daily basis. Therefore, for children and parents or carers who are struggling to adhere to a demanding treatment regimen and in whom DOT may be beneficial, intermittent dosing may be the most pragmatic option. In terms of adherence, the GDG also noted the differences between younger children, in whom ensuring that a sufficient dose is taken is particularly difficult, and older children in their teens. Supervision may therefore be most beneficial in younger children. Although the GDG felt that, in their experience, parents are often the most appropriate people to deliver DOT, this is not always the case, particularly for those in difficult social circumstances. They also noted that this is not an easy task for many parents and that appropriate support needs to be given. According to data from a range of social studies, as well as from their own experience, the GDG was aware that it can be particularly difficult for a person to supervise their own child, and many parents are distressed by the side effects their children may experience whilst taking their antituberculosis chemotherapy. Furthermore, it is important that parents understand that the disappearance of their child's symptoms does not necessarily mean that their child is free of disease, and that they must continue taking their treatment. Given the limitations in the evidence available in children, and the consequent lack of evidence upon which to produce recommendations, the GDG considered the evidence that underpins the standing recommendations for intermittent dosing in adults. When extrapolated to those under the age of 18 it was not felt that the case for recommending the use intermittent dosing in children and young people was enhanced. However, they did agree with the previous guideline's assertion that intermittent dosing should be delivered no less than thrice-weekly, given the wider safety margin for missed doses that is associated with this schedule compared to twice-weekly dosing.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	The evidence comparing intermittent dosing with daily dosing in children with active tuberculosis was not conclusive, although this could be a consequence of the limited data available. Only 4 studies were identified, which were not considered to be methodologically sound, and the quality of evidence for all outcomes was very low. The evidence base suffered from the presence of significant confounding factors and a lack of generalisability to the UK context. A prominent source of confounding was the variation of the intervention and comparator regimens by more than dosing frequency. For example, some papers also varied the duration of treatment in each arm, and some papers varied the combination and number of drugs in each arm. These potentially confounding variables weaken the strength of the evidence for each dosing schedule, and meant that such evidence did not exactly match the interventions and comparators of interest – an issue subsequently reflected in the appraisal of the quality of the evidence.

	Furthermore, a number of the regimens used were not sufficiently similar to the standard regimen of drugs, as recommended by NICEdd. This standard regimen consists of 4 drugs: isoniazid and rifampicin for the full treatment period, supplemented by pyrazinamide and ethambutol for the first 2 months of treatment. Deviation of the regimens under examination from this framework limited the applicability of the evidence to UK practice, a limitation in the evidence that was also reflected in the appraisal of the quality of the evidence. Reporting in many of the studies was poor. For example, details of study designs were often unclear, with the methods used for randomisation, or the use of allocation concealment or blinding, not stated in the text. Unit-of-analysis errors were also common, with analyses not following the intent-to-treat principle. The interventions and comparators used in a number of the studies varied by more than dosing frequency. The intermittent group in the South African RCT received 3 drugs for 2 months, after which the patients received just 2 drugs for the remaining 4 months, whereas the daily group received 3 drugs for the full 6 months, although at a lower dose. The daily group in the Turkish RCT received an additional 3 months of rifampicin, making a total of 12 months of treatment, whereas the intermittent group received just the first 9 months of treatment. And finally, the daily group in 1 of the Indian RCTs received 2 drugs for 9 months, whereas the intermittent group had a total of just 6 months of treatment, but with a higher dose of isoniazid and a greater number of drugs (4 drugs) for the initial 2 months of treatment. Furthermore, the intervention and comparator groups were not balanced at baseline in all of the trials examined. The intermittent group in one of the Indian RCTs had more cavities in at baseline, a sign that the group may have had more severe disease than the daily group at treatment initiation. Additionally, the 'weight for age' and the 'number who were culture positive' was significantly lower in the intermittent group of the South African RCT, which may indicate that the intermittent group were less likely to have tuberculosis, or that their tuberculosis was less severe than the daily group. These confounding factors within both the treatment regimens and the populations studied meant that the GDG did not generally have sufficient confidence in the difference between the estimates of effect having been derived from differences in the dosing schedule alone to use the evidence found in their decision-making. Additionally, the GDG felt that the sample size of the RCT from Turkey (in which n = 36 (with just 4 being bacteriologically confirmed), although only 35 were analysed for the majority of outcomes) and the disaggregated sample sizes for each site of disease in one of the RCTs from India (n (respiratory TB) = 43; n (lymph node TB) = 27; n (disseminated TB) = 6), were too small for the group to have confidence in the papers' estimates of effect. They did not feel able to set a cut-off for sample size as they felt it was still important to review these papers, but unless it was possible to enter this evidence into a meta-analysis, thereby increasing the statistical power of the data, the GDG did not feel that this evidence was helpful in their decision-making. 'Response to treatment', reported in all 4 studies, was considered to be a substitute for outcomes of interest (treatment success and failure, or changes in the signs and symptoms of TB), and, although considered potentially useful to decision-making, the quality of evidence for this outcome was therefore was marked down for indirectness. Additionally, the South African paper reported response to treatment as a score, ranging from -4 to +8. The GDG felt that, although the components that made up the composite score for treatment response (parental assessment, clinical symptoms, weight gain and chest radiograph) were potentially useful, the score itself was not. The disaggregated data for clinical symptoms, weight gain and chest radiograph would have been more helpful to their decision-making.

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dd INSERT REFERENCE TO CG117, and REFERENCE LOCATION OF RECS AND EVIDENCE WITHIN NEW GUIDELINE DOC

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Other considerations	Following review of the available trial evidence, the GDG still did not feel that they had sufficient evidence upon which to produce recommendations. For this reason, they also considered the evidence that informed the 'standing' recommendations for dosing frequency in adults .

4.2.7 Recommendations

56. Do not offer anti-TB treatment dosing regimens of fewer than 3 times per week. [2006, amended 2015]

57. Offer a daily dosing schedule to people with active pulmonary TB. [2006, amended 2015]

58. Consider a daily dosing schedule as first choice in people with active extrapulmonary TB. [2006, amended 2015]

59. Consider 3 times weekly dosing for people with active TB only if:

- risk assessment identifies a need for directly observed therapy and enhanced case management and
- daily directly observed therapy is not possible. **[2006, amended 2015]**

4.3 Dosing schedule in adults with active tuberculosis [2011]

4.3.1 Clinical introduction [2011]

Trials have been conducted on reduced treatment frequency, comparing a daily dosing schedule with higher dosages of drugs given twice or thrice weekly. The aims of these studies were to reduce the total number of doses taken, as both an aid to adherence and treatment monitoring, and to reduce the costs of treatment in resource-poor countries. Intermittent treatment can be given either throughout the initial and continuation phases, or intermittently through the continuation phase after a daily intensive initial phase. Certain drug side effects (for example, 'flu-like syndrome', thrombocytopenia, shock and acute renal failure) are more common when rifampicin is given intermittently rather than daily, and are immunologically mediated. Twice- or thrice-weekly regimens lend themselves more readily to directly observed therapy as they require less frequent monitoring of medication, reducing the costs of supervision if done in a healthcare setting.

4.3.2 Methodological introduction [2011]

A Cochrane systematic review cpared the effectiveness of rifampicin-containing short-course treatment regimens, given twice or thrice weekly, with similar regimens given daily in adult patients with pulmonary TB. Only one RCT performed in Hong Kong was included within the review. The review was methodologically sound; however as it only included one study, this was reviewed separately. This RCT was excluded due to limitations in its methodology.

The Cochrane review included studies where the intermittent arm was any rifampicin-containing multiple drug regimen with a maximum nine month duration, administered up to three times a week with an initial daily dosing phase which could not exceed one month (this was termed 'fully intermittent'). Three further RCTs and a cohort study were identified using similar inclusion criteria, except in terms of the initial daily dosing phase which was broadened to cover studies where this could be two months long, in line with the usual initial intensive treatment phase. Studies could also be intermittent during the intensive phase. The cohort study and one RCT were excluded due to methodological limitations.

None of the studies identified were blinded. Certainly this may have been problematic to achieve in terms of study participants, however those assessing outcomes could potentially have been blinded to treatment allocations.

Very few studies have compared intermittent regimens with daily regimens. Where studies have been conducted, apart from issues of methodology, there are a number of other variables which should be considered when attempting to compare studies and ascertain whether intermittent and daily regimens have equivalent effectiveness. These include whether the intermittent treatment was received during the intensive or continuation treatment phases or during both, the drugs and dosing regimens used, whether treatment was directly observed or self-administered and the frequency of the intermittent regimen (that is, whether once, twice or thrice weekly).

4.3.3 Evidence statements [2011]

In a RCT performed in Africa and Asia, a significantly higher proportion of patients assigned a directly observed daily regimen in the two-month intensive phase rather than a directly observed three times weekly regimen, were culture negative at two months (85% *vs*. 77%, p=0.001). (**1++**)

In a Brazilian RCT there was no significant difference between self-administered six-month treatment regimens, where treatment was daily for the first two months and then either daily or twice weekly during the continuation phase, in terms of the number of bacterial failures or deaths during treatment. (**1+**)

The same study also found no significant difference between daily and twice-weekly regimens in the continuation phase of treatment in terms of adherence (measured by pill counts), relapse rates at 12 months follow up or adverse events. (**1+**)

4.3.4 From evidence to recommendations [2011]

No studies compared twice- or thrice-weekly treatment with daily treatment throughout a six-month regimen, but nevertheless the GDG agreed that twice- and thrice-weekly regimens, with appropriate dosage adjustments, are effective in the treatment of tuberculosis. A single-arm, twice weekly regimen, using rifabutin in HIV-positive individuals with active tuberculosis in the USA (CDC TB Trials Consortium Trial Number 23), was stopped because of the development of acquired rifamycin resistance. In addition to this concern, the twice-weekly regimen is the absolute minimum dosage strategy, and the penalty of missed doses may be increased relapse or treatment failure. For this reason the thrice-weekly regimen, which has a greater safety margin for a few missed doses, is recommended.

Whilst being easier to supervise twice- or thrice-weekly treatment, the large number of different pills (necessarily given as separate formulations), particularly in the initial four-drug phase, can cause nausea and adversely affect adherence. Vomiting as a side effect of rifampicin can be reduced at dosages of 600 mg or more by being taken after breakfast. Flu-like syndromes are more common with intermittent as opposed to daily rifampicin treatment.

The dosages of combination tablets are set for once-daily treatment.

4.3.5 Recommendations

See section 4.2.7

4.4 Duration of treatment in adults with active pulmonary tuberculosis

4.4.1 Clinical introduction

Six months of daily treatment with rifampicin and isoniazid, supplemented in the initial two months with pyrazinamide and either ethambutol or streptomycin (the six-month, four-drug regimen) has been the gold standard for the treatment of active tuberculosis disease for at least the last 25 years. Attempts have been made to shorten the total duration of treatment by reducing the duration of the continuation phase. It is hoped that this will ease the treatment burden for the patient and improve adherence without sacrificing the ability of regimens to achieve cure and prevent relapse.

4.4.2 Review question

In adults with drug susceptible, active pulmonary TB receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?
ii) ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

4.4.3 Evidence review

This evidence review focused on the most effective duration of chemotherapeutic treatment in adults with active pulmonary tuberculosis. Duration of treatment for this population can be broadly grouped into three categories:

- 6 months of treatment: the currently recommended length of treatment
- less than 6 months of treatment
- more than 6 months of treatment.

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the duration of chemotherapeutic treatment for drug susceptible, active pulmonary TB in adults. Only randomised and quasi-randomised controlled trials were considered for inclusion. Papers of interest were those that compared one duration of treatment with another. (See appendix C for the full review protocol).

Trials were excluded if:

- the population included children (under 18 years of age);
- the population included people with active extrapulmonary TB, latent TB or drug resistant TB;
- the paper focused primarily on populations with comorbidities or coexisting conditions (other than HIV) that will affect the choice or management of treatment;
- the intervention did not contain at least 3 drugs in the initial phase;
- the intervention did not contain rifampicin throughout;
- the intervention included drugs not licensed in the UK; or
- observational studies, case series, case studies, and narrative reviews.

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From a database of 2762 abstracts, 234 full-text articles were ordered and 17 papers describing 12 primary studies met the inclusion criteria. Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used Review Manager to meta-analyse the data into pooled effect estimates. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

4.4.4 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 822 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

4.4.5 Evidence statements

Very low quality evidence from 2 randomised controlled trials found less than 6 months of treatment to be associated with higher rates of relapse than 6 months of treatment in smear-positive patients.

Very low quality evidence from 2 randomised controlled trials comparing 6 months and more than 6 months of treatment in smear-positive patients was inconclusive about which duration of treatment was the most effective in reducing the incidence of treatment failure and relapse, and in terms of achieving cure.

Very low quality evidence from 3 randomised controlled trials comparing less than 6 months and 6 months of treatment in smear-negative patients was inconclusive about which duration of treatment was the most effective in reducing the incidence of treatment failure, relapse and adverse events, and in terms of improving the signs and symptoms of disease.

Very low quality evidence from 2 randomised controlled trials comparing 6 months and more than 6 months of treatment in patients with HIV coinfection was inconclusive about which duration of treatment was the most effective in reducing mortality, treatment failure, relapse and adverse events, and in terms of achieving cure and promoting adherence.

4.4.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), relapse and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. There was some debate over whether mortality, a rare but severe outcome, was more important than cure. From a patient perspective, mortality is likely to be the most important outcome, whereas cure is more clinically useful in guiding decisions regarding treatment options. Changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although ‘response to treatment’ was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of TB. 'Recurrence' was also not a predefined outcome of interest, though it was considered a potentially useful substitute for relapse.
Trade-off between benefits and harms	The aim of using less than 6 months treatment is to minimise inconvenience to the patient and improve their quality of life. Shorter regimens are associated with fewer adverse events related to drugs than longer regimens, largely because overall exposure to drugs is higher but also because prolonged treatment means that the need for additional medications during treatment is more likely to

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arise, increasing the risks of drug-drug interactions. However, shorter regimens also theoretically carry an increased risk of relapse and resistance. Thus the aim of prescribing drugs at longer durations is to minimise the risk of relapse and resistance, though there is a potential worsening effect on adherence and the patient's quality of life. In addition the chances of prescribing errors rise with the duration of treatment.

12 RCTs, reported across 17 papers, comparing different durations of treatment in adults with pulmonary TB were identified. The population within the evidence base could be differentiated by the severity of disease, as defined by the smear, culture or radiographic status of the patient, and by their HIV status.

Patients with smear-positive, culture-positive disease:

The GDG noted that there was a higher incidence of relapse and radiographic deterioration amongst smear-positive patients receiving the less than 6 months of treatment than amongst those receiving 6 months of treatment. They felt that this evidence, from 2 RCTs, suggested that less than 6 months of treatment is insufficient in smear-positive, culture-positive patients.

The GDG also discussed the evidence, extracted from 2 RCTs, that compared 6 months of treatment with more than 6 months of treatment in smear-positive populations. They noted that the estimates of effect were not significantly different for any of the outcomes recorded, including treatment failure, relapse and cure. Additionally, the GDG felt that, in their experience, 6 months of treatment had been effective in the patients they had managed.

For these reasons, the GDG decided to recommend 6 months of treatment in patients with active, smear-positive tuberculosis.

Patients with smear-negative, culture-positive disease:

The GDG also discussed the evidence, extracted from 3 RCTs, that compared less than 6 months of treatment with 6 months of treatment in smear-negative, culture-positive populations. They noted that the estimates of effect were not significantly different for treatment failure, radiographic status and relapse, and fewer adverse events were experienced among those receiving shorter durations.

Although promising, the GDG did not feel that the evidence was sufficiently conclusive to enable them to make a recommendation for shortening treatment to less than 6 months in this population. The evidence had numerous methodological limitations, including, for example, the fact that the 6-month group in 1 study all received intermittent therapy, whereas the 3- and 4-month groups received daily therapy at the same doses. That is, the regimen in the 6-month group was less intensive than the regimens in the less-than-6-month groups. Additionally, although the populations studied were larger than in many of the other studies included in this review, the GDG did not feel that the sample sizes were large enough to detect differences between the treatment durations. Event rates for treatment failure and relapse would be expected to be low in smear-negative patients, therefore very large trials would be needed to observe a difference in effect or to conclude that the durations were equally effective.

The GDG noted that there are other regimens available that have shown promise in reducing the duration of treatment. However, since these regimens include drugs outside the standard recommended combination of isoniazid, rifampicin, ethambutol and pyrazinamide – most notably moxifloxacin – they were not within the scope of this guideline, and therefore not reviewed here.

Patients with cavitatory disease:

1 RCT examined 9 months and 18 months of treatment in patients with cavitatory disease (cavities >2 cm). Again, it was noted that there the regimens lacked pyrazinamide and that there was a low level of drug resistance at baseline.

Data was available for treatment failure, as well as relapse and those who were 'alive and well' after 54 months of follow-up, although none demonstrated a

	statistically significant difference between 9 and 18 months of treatment. Although the GDG found it reassuring that 18 months of treatment was not clearly better, they also noted that 18 months of treatment is not generally considered as an option for this population, and for this reason they did not feel the comparison of 9 months and 18 months of treatment to be an appropriate or useful one. A comparison of 6 months and 9 months of treatment would have been more informative to their decision-making. **Patients with non-cavitatory disease:** 1 RCT examined 6 months and 12 months of treatment in patients with no cavities, or no cavities >2 cm. The GDG noted that the estimates of effect were not significantly different for treatment failure or the number to be 'alive and well' after 54 months of follow-up, although relapse demonstrated a significant difference between 6 and 12 months of treatment, with more occurring in the 6-month group. However, the relapse rate was low and the sample size was small, decreasing confidence in the effect observed. Additionally, the group noted that the regimens did not include pyrazinamide, a key component of the standard recommended regimen, limiting the informativeness of the relapse rates observed. The group also noted that there was a low level of drug resistance at baseline (3.4%). These limitations meant that, based on the available evidence, the GDG did not feel that it would be appropriate to extend treatment beyond 6 months in patients with non-cavitatory disease. This decision was further supported by the success of 6-month regimens in their own experience. **HIV-positive patients:** The GDG discussed the evidence, extracted from 2 RCTs, that compared 6 months of treatment with more than 6 months of treatment in HIV-positive patients. They noted that the estimates of effect were not significantly different for any of the outcomes recorded, including mortality, cure, treatment failure, relapse, adverse events and adherence. The GDG also noted that treatment was intermittent in one of the papers, whereas usual practice in the UK for patients with HIV is a daily regimen. The applicability of this evidence was further limited by the fact that the prescribed doses were lower than recommended. However, these factors would have tempered the effectiveness of the 6-month regimen, and therefore the fact that it performed as well as the 9-month regimen is reassuring. Additionally, in their experience, 6 months of treatment has been effective in patients with HIV. The GDG acknowledged the desirability of shortening regimens where possible. This is because antituberculosis treatment currently poses a significant burden to patients, with the long duration having a negative impact upon patients' quality of life. Longer durations can also be difficult to fully adhere to for many patients, impeding the achievement of cure and also increasing the risk that drug resistant disease may emerge. Despite this, the GDG also felt it was critical to ensure that these regimens were effective in achieving, and maintaining, cure. Overall, the GDG felt that there is currently insufficient evidence to recommend a shortening of treatment duration to less than 6 months in any patient. However, they noted that the data available for regimens of less than 6 months of treatment in smear-negative patients was promising, and that further evidence would be useful in future considerations concerning the shortening of antituberculosis treatment. For the reasons outlined above, the GDG also felt it was important that patients did not have their treatment extended beyond 6 months unnecessarily. They felt that more evidence on which specific patients might benefit from treatment regimens of more than 6 months, and by extension which patients should not have their treatment extended beyond 6 months, would also be valuable in future considerations regarding the duration of antituberculosis treatment
Trade-off between net	None identified

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health benefits and resource use	
Quality of evidence	The evidence base suffered from the presence of significant confounding factors and a lack of generalisability to the UK context. A notable source of possible confounding was the variation of the intervention and comparator regimens by more than duration. This weakened the strength of the limited evidence available, meaning that it did not exactly match the intervention of interest, an issue subsequently reflected in the appraisal of the quality of the evidence. Furthermore, the regimens used did not use the standard regimen of drugs, as recommended by NICE . This standard regimen consists of 4 drugs: isoniazid and rifampicin for the full treatment period, supplemented by pyrazinamide and ethambutol for the first 2 months of treatment. Deviation of the regimens under examination from this framework limited the applicability of the evidence to UK practice; this was also reflected in the appraisal of the quality of the evidence. Only 1 study was identified that included respiratory sites beyond pulmonary disease. This study examined 6 months and 9 months of treatment in patients with TB and HIV coinfection; 9% of patients had TB in pleural or lymph node sites, with the remaining 91% having pulmonary disease. Overall, the quality of evidence for all outcomes was defined as ‘very low’. There were a number of issues with the interventions used that made the evidence less directly applicable to UK practice: most commonly, the regimens did not use all of or just the 4 standard recommended drugs, but in some trials the regimens in the two groups did not differ by treatment duration alone. Additionally, the doses used in a number of studies were not in line with those recommended by the British National Formulary. In addition to the 'indirectness' arising from issues relating to the interventions used, indirectness was also introduced by a number of papers due to the inclusion of a small proportion of patients with single or combined drug resistance at baseline. These patients can be more difficult to treat and may be confounding the estimates of treatment effect for patients with drug susceptible disease (the population of interest in this review). In addition to this, many of the papers were not adults-only, with inclusion criteria for the trials often set at those above 12 or 15 years of age. The GDG also felt that the age of the studies may further reduce the applicability of the evidence because of changes in practice over time. Furthermore, many of the studies were performed in countries (including India, Pakistan, Singapore and Zaire) that, at the time, had significantly different epidemiological profiles to the UK today, with high prevalences of both TB and HIV infection. Although 2 studies explicitly examined duration of treatment in patients with TB and HIV coinfection, it is unclear if the populations in the remaining 10 studies were all HIV-negative, if they were all HIV-positive, or if the population had a mix of HIV statuses. Furthermore, the use of antiretroviral therapy or not can also influence the estimates of effect and the generalisability of the evidence to the UK context: patients on antiretroviral therapy have better outcomes than those with TB who are not, though the applicability of this in England and Wales is unclear. A wide variety of diagnostic criteria were applied across the studies, both at baseline to assess patients for entry into the study and as a means of assessing treatment outcome. This means that pooling data from multiple studies suffered from heterogeneity, both in terms of the populations covered and the definitions of outcome. The different regimens of drugs used in each study further contributed to the heterogeneity present. Additionally, a number of substitute outcomes were extracted by the reviewer, including 'response to treatment' and 'recurrence'. ‘Response to treatment' was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure, although the exact focus of the outcome definitions used varied widely and often also incorporated changes in the signs and symptoms of disease. 'Recurrence’ was considered to be a substitute for relapse. Although potentially useful in the absence of data for 'true' relapse, data on recurrence can be difficult to interpret as its definition generally does not

	distinguish between recurrence of the disease due to relapse and recurrence of the disease due to reinfection. In studies conducted in settings with a high prevelance of TB, the usefulness of recurrence data is particularly limited since the risk of reinfection may be high. There was a significant lack of methodological detail in many of the papers, including a lack of information about the method of randomisation used, or whether or not allocation concealment and blinding were used. This means that the risk of bias in the trials is difficult to appraise, and the quality of evidence was downgraded. Follow-up was also an issue in a large number of trials in that it was often measured from treatment initiation. This meant that, for outcomes for which follow-up extends beyond treatment completion (most notably relapse, but also mortality and long-term changes in the signs and symptoms of tuberculosis), follow-up was for different periods of time in the intervention and comparator groups because different durations of treatment were used. Additionally, the loss of patients to follow-up was also not consistently reported, therefore the impact of this on inconsistency was not always possible to appraise. The GDG was also concerned with the small sample sizes used in a number of studies, further reducing the sensitivity to detect differences in the effectiveness of different treatment durations. The small number of events recorded support the suggestion that the included studies were underpowered.
Other considerations	

4.4.71 Recommendations

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60. Once a diagnosis of active TB is made:

- the clinician responsible for care should refer the person with TB to a clinician with training in, and experience of, the specialised care of people with TB
- the TB service should include specialised nurses and health visitors
- TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised clinician.

  If these arrangements are not possible, seek advice from more specialised colleagues throughout the treatment period. **[2015]**

61. For people with active TB without central nervous system involvement, offer:

- isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, then
- isoniazid and rifampicin for a further 4 months.

  Modify the treatment regimen according to drug susceptibility testing. **[2015]**

4.5 Duration of treatment in children and young people with active pulmonary tuberculosis

4.5.1 Review question

In children and young people with drug susceptible, active pulmonary TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?

ii) ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

4.5.2 Evidence review

This evidence review focused on the most effective duration of chemotherapeutic treatment in children with active pulmonary tuberculosis. Duration of treatment for this population can be broadly grouped into three categories:

- 6 months of treatment: the currently recommended length of treatment
- less than 6 months of treatment
- more than 6 months of treatment.

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the duration of chemotherapeutic treatment for drug susceptible, active pulmonary TB in children. Only controlled trials were considered for inclusion, first at the randomised and quasi-randomised levels, and subsequently at the non-randomised level due to the paucity of evidence in this area. Papers of interest were those that compared one duration of treatment with another. (See appendix C for the full review protocol).

Trials were excluded if:

- the population included adults (aged 18 years or more);
- the population included children and young people with active extrapulmonary TB, latent TB or drug resistant TB;
- the paper focused primarily on populations with comorbidities or coexisting conditions (other than HIV) that will affect the choice or management of treatment;
- the intervention did not contain at least 3 drugs in the initial phase;
- the intervention did not contain rifampicin throughout;
- the intervention included drugs not licensed in the UK; or
- observational studies, case series, case studies, and narrative reviews.

From a database of 2762 abstracts, 229 full-text articles were ordered and 1 paper describing 1 primary study met the inclusion criteria (Kansoy et al, 1996). Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used Review Manager to meta-analyse the data into pooled effect estimates. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

In addition to a lack of relevant trials, the evidence base suffered from the presence of significant confounding factors and a lack of generalisability to the UK context. A notable source of possible confounding was the variation of the intervention and comparator

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regimens by more than duration. This weakened the strength of the limited evidence available, meaning that it did not exactly match the intervention of interest – an issue subsequently reflected in the appraisal of the quality of the evidence.

Furthermore, the regimens used did not use the standard regimen of drugs, as recommended by NICE. This standard regimen consists of 4 drugs: isoniazid and rifampicin for the full treatment period, supplemented by pyrazinamide and ethambutol for the first 2 months of treatment. Deviation of the regimens under examination from this framework limited the applicability of the evidence to UK practice; this was also reflected in the appraisal of the quality of the evidence.

4.5.3 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 822 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

4.5.4 Evidence statements

Very low quality evidence from 1 randomised controlled trial comparing 9 months and 12 months of treatment in 36 patients was inconclusive about which was the most effective treatment duration in terms of reducing the incidence of recurrence or hepatotoxicity in children with active TB, and in terms of increasing adherence to treatment.

4.5.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (also encompassing treatment success and treatment failure), relapse and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. There was some debate over whether mortality, a rare but severe outcome, was more important than cure. From a patient perspective, mortality is likely to be the most important outcome, whereas cure is more clinically useful in guiding decisions regarding treatment options. Changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were also considered important for decision-making. Although 'recurrence' was not a predefined outcome of interest, it was considered to be a useful substitute for relapse.
Trade-off between benefits and harms	1 RCT was found that compared 9 months and 12 months of treatment in children with pulmonary TB. The paper reported data for the incidence of recurrence in the 12 months after treatment completion, the incidence of hepatotoxicity and adherence (the number excluded by the authors due to "poor compliance"). The results were inconclusive, with no statistically significant difference produced between the 2 treatment durations. Given the limited evidence available in children, the GDG felt it was appropriate to extrapolate that found in adults and to adopt the recommendations made.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	Overall, the quality of evidence for all outcomes was defined as 'very low'. As with the review conducted in adults, there were a number of issues with the interventions used that made the evidence less directly applicable to the question of which duration of treatment should be prescribed to children in the UK: the regimens in the two groups did not differ by treatment duration alone,

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	and the regimens did not use all of or just the 4 standard recommended drugs. The regimens contained streptomycin and were missing pyrazinamide and ethambutol. Additionally, the doses of isoniazid and streptomycin that were used were above that recommended for use in children by the British National Formulary. The impact of this 'indirectness' on the quality of evidence was considered to be 'very serious'. Furthermore, 'recurrence' was considered to be a substitute for the outcome of interest (relapse). Its definition generally does not distinguish between recurrence of the disease due to relapse and recurrence of the disease due to reinfection. Additionally, although described as 'randomised', the authors do not provide information as to the method used, nor about the use of allocation concealment, blinding, or the definitions of hepatotoxicity or adherence that were used. The risk of bias was defined as 'very serious'. Due to the small sample size used (n = 36), the data also suffered from imprecision.
Other considerations	

4.5.6 Recommendations

See section 4.4.7

4.6 Duration of treatment in people with active extrapulmonary tuberculosis

4.6.1 Clinical introduction

This evidence review focused on the most effective duration of chemotherapeutic treatment in people with active extrapulmonary tuberculosis. Duration of treatment for those with active tuberculosis without central nervous system (CNS) involvement can be broadly grouped into three categories:

- 6 months of treatment: the currently recommended length of treatment
- less than 6 months of treatment
- more than 6 months of treatment.

Due to the severe consequences of CNS involvement, duration of treatment for those with active tuberculosis with CNS involvement is generally much longer. Duration of treatment in this population can be broadly grouped into three categories:

- 12 months of treatment: the currently recommended length of treatment
- less than 12 months of treatment
- more than 12 months of treatment.

4.6.2 Review question

In people with drug susceptible, active extrapulmonary tuberculosis receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity?

- Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?
- Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

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4.6.13 Evidence review

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the duration of chemotherapeutic treatment for drug susceptible, active TB in any extrapulmonary site. Only controlled trials were considered for inclusion, first at the randomised and quasi-randomised levels, and subsequently at the non-randomised level due to the paucity of evidence in this area. The GDG also requested that for the most 'severe' sites of extrapulmonary TB (CNS, pericardial and disseminated (including miliary) tuberculosis) the reviewer also collect prospective observational evidence. Papers of interest were those that compared one duration of treatment with another. (See appendix Cfor the full review protocol).

Trials were excluded if:

- the population included people with active pulmonary tuberculosis, latent tuberculosis or drug resistant tuberculosis;
- the paper focused primarily on populations with comorbidities or coexisting conditions (other than HIV) that will affect the choice or management of treatment;
- the intervention did not contain at least 3 drugs in the initial phase;
- the intervention did not contain rifampicin throughout;
- the intervention included drugs not licensed in the UK; or
- observational studies (except for the 3 sites listed above), case series, case studies, and narrative reviews.

The original literature search produced a database of 2762 abstracts. 229 full-text articles were ordered, and 12 papers describing 8 primary studies met the inclusion criteria. These included 2 non-randomised controlled trials for CNS tuberculosis (Doğanay et al, 1995; Jacobs et al, 1992), 2 RCTs described in 3 papers for spinal tuberculosis (Darbyshire,1999; Griffiths et al, 1986; Upadhyay et al, 1995), 4 RCTs described in 5 papers for lymph node tuberculosis (Al-Aska et al, 1992; Campbell et al, 1985; Campbell et al, 1988; Campbell et al, 1993; Yuen et al, 1997), and 2 RCTs for gastrointestinal tuberculosis (Kim et al, 2003; Park et al, 2009). No papers were found that examined the duration of treatment in people with non-spinal bone and joint tuberculosis, pericardial tuberculosis, genitourinary tuberculosis or disseminated (including miliary) tuberculosis. The additional observational searches conducted for CNS, pericardial and disseminated (including miliary) tuberculosis produced a database of 389 abstracts. 42 full-text articles were ordered, but none met the inclusion criteria.

Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used Review Manager to meta-analyse the data into pooled effect estimates. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

4.6.14 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 822 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

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4.6.5 Evidence statements

People with active central nervous system tuberculosis

Very low quality evidence from 2 non-randomised trials comparing 6 months and 9 months of treatment, and 8 months and 12-16 months of treatment, was inconclusive about which was the most effective treatment duration to reduce mortality, relapse, neurological sequelae and adverse events in people with active meningeal tuberculosis.

People with active spinal tuberculosis

Very low quality evidence from 2 randomised controlled trials (reported across 3 papers) comparing 6 months and 9 months of treatment was inconclusive about which was the most effective treatment duration to reduce mortality, relapse, and adverse events in people with active spinal tuberculosis, and in terms of increasing treatment success or improving signs and symptoms.

People with active non-spinal bone and joint tuberculosis

No studies were identified that met the inclusion criteria.

People with active pericardial tuberculosis

No studies were identified that met the inclusion criteria.

People with active lymph node tuberculosis

Very low quality evidence from 4 randomised controlled trials (reported across 5 papers) comparing 6 months and 9 months (2 studies), 9 months and 12 months (1 study), and 9 months and 18 months (1 study) of treatment was inconclusive about which was the most effective treatment duration to reduce relapse, treatment failure and adverse events in people with active lymph node tuberculosis, and in terms of increasing treatment success or improving signs and symptoms.

People with active gastrointestinal tuberculosis

Very low quality evidence from 2 randomised controlled trials comparing 6 months and 9 months, and 9 months and 15 months of treatment, was inconclusive about which was the most effective treatment duration to reduce treatment failure, relapse and adverse events in people with active lymph node tuberculosis, and in terms of increasing treatment success.

People with active genitourinary tuberculosis

No studies were identified that met the inclusion criteria.

People with active disseminated (including miliary) tuberculosis

No studies were identified that met the inclusion criteria.

4.6.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), relapse and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision making. There was some debate over whether mortality, a rare but severe outcome, was more important than cure. From a patient perspective, mortality is likely to be the most important outcome, whereas cure is more clinically useful in guiding decisions regarding

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	treatment options. Changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of TB. 'Recurrence' was also not a predefined outcome of interest, though it was considered a potentially useful substitute for relapse.
Trade-off between benefits and harms	**Central nervous system tuberculosis:** The GDG discussed the evidence available for the duration of treatment in patients with TB of the CNS (2 non-randomised trials) and noted both its paucity, even after the performance of an additional literature search for prospective observational studies, and the significant limitations in its quality and generalisability. Together, these issues meant that the GDG was unable to confidently draw conclusions from the evidence with regards to which duration of treatment is most effective in this population. The GDG subsequently noted that, according to the most recent HPA/PHE data, there are only 87 cases of CNS TB in the UK; they felt that the rarity of this condition may explain the paucity of trial data. Given the severe consequences of not adequately treating CNS TB, the GDG felt that strong evidence would be required to reduce the duration of treatment to less than the currently recommended 12 months. The available evidence did not meet this burden of proof, so the GDG felt that the duration of treatment for CNS TB should remain at 12 months. This decision was, they felt, supported by the success of 12-month regimens in their own experience. **Spinal tuberculosis:** The GDG discussed the evidence available for the duration of treatment in patients with spinal TB (2 RCTs), and noted that the estimates of effect were not significantly different between 6 months and 9 months of treatment for any of the outcomes recorded, including mortality, changes in signs and symptoms, response to treatment, relapse and adverse events. However, they also noted the small samples used in the trials, and felt that these may explain the failure of the studies to detect a difference in effect. The small size of the samples studied also meant that the GDG was cautious in concluding that the 2 durations were equivalent. Despite the fact that the evidence was inconclusive, the GDG felt that it was noteworthy that 6 months appeared to be as effective as a longer duration of treatment across all outcomes. Additionally, the GDG felt that, in their experience, 6 months of treatment had been effective in the patients they had managed. For this reason, the GDG decided to uphold the previous recommendation for 6 months of treatment in patients with spinal tuberculosis without CNS involvement. A comprehensive systematic review into the treatment of children with osteoarticular tuberculosis (Donald, 2011) was discussed. It was felt that the review's conclusion that 6 months of treatment in children and adults with osteoarticular TB is sufficient further supports the GDG's consensus that extending the duration of treatment beyond 6 months of treatment is not necessary for spinal TB without CNS involvement. It was noted that a major issue amongst people with spinal TB is that diagnosis, or the initiation of diagnostic procedures, is often delayed due to the non-specific presentation of the disease – often back pain, for which TB is unlikely to be the first suspicion. This means that the disease may have progressed to a more advanced stage, with a greater deterioration in kyphosis and vertebral loss, by the time treatment is initiated. Decreasing the time to diagnosis and, in particular, the time to treatment initiation are critical in preventing long term damage to the spine, as well as in ensuring treatment success. The deterioration of the spine in spinal TB can often leave a patient with long term bending of the spine, fusion of vertebrae, back pain or other residual effects. Although this can be concerning for both patient and clinician, the GDG

emphasised that this is not an automatic reason for extending treatment beyond 6 months, as after 6 months of treatment these residual effects are not generally the result of persistent disease. Rather, they are the continued effects of previous deterioration when the disease was still present, and should be examined and dealt with by surgery or other interventions. It was felt that this point also highlights the importance of a multidisciplinary team in the management of patients with spinal TB.

It was noted that one other possible reason for the extension of treatment beyond 6 months in the past is perhaps the idea that the penetration of drugs into the disc space is conceivably more limited than for other sites of the body due to the vascularisation of this area. However, the GDG did not feel that this was a strong enough reason to recommend an extension of treatment in people with spinal TB beyond 6 months.

Non-spinal bone and joint tuberculosis:

No evidence was identified for non-spinal bone and joint TB.

Taking into consideration the evidence for spinal TB, as well as the success of 6-month regimens in their own experience, meant that the GDG felt comfortable in reissuing a recommendation for 6 months of treatment for people with bone and joint TB.

Pericardial tuberculosis:

No evidence was identified for pericardial TB, even after the performance of an additional literature search for prospective observational studies.

It was felt that the rationale underpinning the previous recommendation of 6 months of treatment ─ that pericardial is a pauci-bacillary form of extrapulmonary disease, and extrapolation from other forms of extrapulmonary disease with more evidence suggests that a six-month duration of treatment is effective ─ is still appropriate.

Lymph node tuberculosis:

The GDG discussed the evidence available for the duration of treatment in patients with lymph node TB (4 RCTs), and noted that the estimates of effect were not significantly different between 6 months and 9 months of treatment for any of the outcomes recorded, including changes in signs and symptoms, response to treatment, relapse and adverse events. However, they once again noted the small samples used in the trials, and felt that these meant that they could not conclusively rule out a difference in effect, nor confidently conclude that the 2 durations were equivalent, based on the evidence alone. Despite this, the GDG felt that, in their experience, 6 months of treatment had been effective in the patients they had managed. For this reason, the GDG decided to uphold the previous recommendation for 6 months of treatment in patients with lymph node TB.

It was also noted, however, that both 6 months and 9 months of treatment were associated with a relatively high relapse rate (8.9% and 7.7%, respectively). Relapse is considered by the GDG to be a critical outcome, but they felt that this was not sufficient evidence to extend treatment beyond 6 months. One reason for this is that the definition of relapse used within the studies was clinical, rather than confirmed microbiologically. That is, it was based upon the emergence of newly enlarged nodes or the appearance of sinuses or abscesses, or the persistence of previously enlarged nodes, sinuses or abscesses. These residual effects are common in people with previous lymph node TB, particularly in those who have experienced immune restitution inflammatory syndrome in which a rapid restoration or surge in immune response leads to deterioration in the patient's clinical condition. Although this can be concerning for both patient and clinician, the GDG emphasised that treatment should not be extended beyond 6 months in patients without microbiologically confirmed treatment failure or relapse. It was felt that this is an important area for both patients and clinicians to understand, and may be an area in which support and education activities could be of assistance.

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	The GDG felt that there were no concerns over drug penetration in patients with lymph node TB that would theoretically support an extension of treatment beyond 6 months. Additionally, in their experience, 6 months of treatment had been effective in the patients they had managed. **Gastrointestinal tuberculosis:** The GDG discussed the evidence available for the duration of treatment in patients with gastrointestinal TB (2 RCTs), and noted that the estimates of effect were not significantly different between 6 months and 9 months of treatment for any of the outcomes recorded, including response to treatment, relapse and adverse events. However, they once again noted the small samples used in the trials, and felt that these meant that they could not conclusively rule out a difference in effect, nor confidently conclude that the 2 durations were equivalent, based on the evidence alone. Despite this, the GDG felt that, in their experience, 6 months of treatment had been effective in the patients they had managed. Additionally, the GDG felt that there were no concerns over drug penetration in patients with gastrointestinal TB that would theoretically support an extension of treatment beyond 6 months. For these reasons, the GDG decided to uphold the previous recommendation for 6 months of treatment in patients with gastrointestinal TB. **Genitourinary tuberculosis**: No evidence was identified for genitourinary TB. Taking into consideration the evidence for gastrointestinal TB, which as another area of soft tissue TB was felt to be to some degree informative, the GDG felt comfortable in reissuing a recommendation for 6 months of treatment for people with genitourinary TB. This was further supported by the success of 6-month regimens in the GDG's own experience. **Disseminated (including miliary) tuberculosis:** No evidence was identified for disseminated (including miliary) TB, even after the performance of an additional literature search for prospective observational studies. As noted by the previous GDG during the formulation of the current recommendation for duration of treatment for people with disseminated TB, all sites outside the CNS for which data exist show adequate response to a six-month regimen, whereas six-month regimens have not been shown to be adequate for those with CNS involvement. Exclusion of CNS disease is important, so that the correct duration of treatment is applied. Disseminated TB without CNS involvement should be treated as for other sites of TB without CNS involvement (that is, with 6 months of treatment), whereas disseminated TB with CNS involvement should follow the recommendation made for CNS TB (12 months of treatment).
Trade-off between net health benefits and resource use	Owing to the poor quality and quantity of clinical evidence, and the fact that no health economic evidence was returned from the searches, the GDG was unable to consider in detail whether there would be any trade-offs between net health benefits and resource use for this question. The GDG recognised that these are less common manifestations of TB, and the drugs used to treat them (and the durations over which they are prescribed) are broadly in common with other forms of the disease. It is therefore expected that the resource implications of these recommendations would be minimal.
Quality of evidence	The evidence base in this area is hampered by the difficulty of recruiting patients for participation in studies. Mostly the existing studies included people following a presumptive diagnosis with few positive culture confirmations. There is no evidence to support treatment durations of less than 12 months in people with central nervous system tuberculosis. All the evidence on duration has some methodological limitations. Given the serious risk of disability and mortality,

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the 12 months of antituberculosis treatment remains appropriate.

There is also no evidence to inform the choice of drugs. Caution is required with ethambutol in unconscious patients, but the important factor in drug choice is penetration into the CSF. Ethionamide, isoniazid, prothionamide and pyrazinamide achieve best penetration. Rifampicin is less good in this regard, and ethambutol and streptomycin only penetrate into CSF if the meninges are inflamed.

No evidence was found for non-spinal bone and joint TB, pericardial TB, genitourinary TB, or disseminated (including miliary) TB. Additionally, no evidence was found for shortenning treatment to durations of less than those that are currently recommended ─ 6 months for TB without CNS involvement, and 12 months for TB with CNS involvement.

Where evidence was available, little was found to suggest that one duration of treatment is significantly better than another, although it was also not possible to state conclusively that different durations are equivalent in their effectiveness. It was felt that the poor quality of the evidence played a significant role in the inconclusive nature of the evidence; overall, the quality of evidence for all outcomes was defined as ‘very low’.

There were a number of issues with the interventions used that made the evidence less directly applicable to UK practice: most commonly, the regimens did not use all of or just the 4 standard recommended drugs, but in some trials the regimens in the two groups did not differ by treatment duration alone. Additionally, the doses used in a number of studies were not in line with those recommended by the British National Formulary.

In addition to the 'indirectness' arising from issues relating to the interventions used, indirectness was also introduced by a number of papers due to the inclusion of a small proportion of patients with single or combined drug resistance at baseline. These patients can be more difficult to treat and may be confounding the estimates of treatment effect for patients with drug susceptible disease (the population of interest in this review).

The GDG also felt that the age of the studies may further reduce the applicability of the evidence because of changes in practice over time. Furthermore, many of the studies were performed in countries (including India, Pakistan, Singapore, Thailand and Turkey) that, at the time, had significantly different epidemiological profiles to the UK today, with high prevalences of both TB and HIV infection.

A wide variety of diagnostic criteria were applied across the studies, both at baseline to assess patients for entry into the study and as a means of assessing treatment outcome. This means that pooling data from multiple studies suffered from heterogeneity, both in terms of the populations covered and the definitions of outcome. The different regimens of drugs used in each study further contributed to the heterogeneity present.

Additionally, a number of substitute outcomes were extracted by the reviewer, including 'response to treatment' and 'recurrence'. ‘Response to treatment' was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure, although the exact focus of the outcome definitions used varied widely and often also incorporated changes in the signs and symptoms of disease. 'Recurrence’ was considered to be a substitute for relapse. Although potentially useful in the absence of data for 'true' relapse, data on recurrence can be difficult to interpret as its definition generally does not distinguish between recurrence of the disease due to relapse and recurrence of the disease due to reinfection.

There was a significant lack of methodological detail in many of the papers, including a lack of information about the method of randomisation used, or whether or not allocation concealment and blinding were used. This means that the risk of bias in the trials is difficult to appraise, and the quality of evidence was downgraded.

Follow-up was also an issue in a large number of trials in that it was often measured from treatment initiation. This meant that, for outcomes for which follow-

	up extends beyond treatment completion (most notably relapse, but also mortality and long-term changes in the signs and symptoms of tuberculosis), follow-up was for different periods of time in the intervention and comparator groups because different durations of treatment were used. Additionally, the loss of patients to follow-up was also not consistently reported, therefore the impact of this on inconsistency was not always possible to appraise. The GDG was also concerned with the small sample sizes used across most of the studies, further reducing the sensitivity to detect differences in the effectiveness of different treatment durations. The small number of events recorded support the suggestion that the included studies were underpowered.
Other considerations	

4.6.17 Recommendations

62. For people with active TB of the central nervous system, offer:

- isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, then
- isoniazid and rifampicin for a further 10 months.

Modify the treatment regimen according to drug susceptibility testing. **[2015]**

63. Test people with active spinal TB who have neurological signs or symptoms for central nervous system involvement. Manage direct spinal cord involvement (for example, a spinal cord tuberculoma) as TB of the central nervous system. [2015]

64. For people with active spinal TB without central nervous system involvement, do not extend treatment beyond 6 months for residual effects (for example, persistent bending of the spine or vertebral loss). [2015]

65. Test people with disseminated (including miliary) TB for central nervous system involvement. If there is evidence of central nervous system involvement, treat as for TB of the central nervous system. [2015]

66. Treat active peripheral lymph node TB in people who have had an affected gland surgically removed with the standard recommended regimen. [new 2015]

67. For people with active TB of the lymph nodes, do not routinely extend treatment beyond 6 months for newly enlarged lymph nodes or sinus formation, or for residual enlargement of the lymph nodes or sinuses. [new 2015]

4.7 Use of adjunctive corticosteroids in the treatment of active tuberculosis

4.7.1 Clinical introduction

It is thought that corticosteroids may confer benefit through the prevention of the tissue damage that tuberculosis can cause through bringing about an immune-mediated inflammatory response. The corticosteroids most commonly used in people with tuberculosis are prednisolone and dexamethasone, although others have included methylprednisolone, triamcinolone, hydrocortisone, adrenocorticotropic hormone and cortisol. This evidence review focused on the effectiveness of adding corticosteroids to the antituberculosis regimens prescribed to people with active tuberculosis.

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4.7.2 Review question

In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), do corticosteroids as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

4.7.3 Evidence review

For this review question, papers were identified from a number of different databases (Medline, Medline in Process, Embase, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the use of corticosteroids in addition to antituberculosis chemotherapy in patients with active tuberculosis.

Only controlled trials were considered for inclusion, first at the randomised and quasi-randomised levels, and subsequently at the non-randomised level due to the paucity of evidence in this area. Papers of interest were those that compared the use of antituberculosis chemotherapy plus a corticosteroid against antituberculosis chemotherapy alone, with a placebo or with another corticosteroid in people with drug susceptible or drug resistant active tuberculosis. (See Appendix C for the full review protocol).

Trials were excluded if they included:

- people with latent tuberculosis;
- people receiving corticosteroids in the absence of antituberculosis chemotherapy;
- papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment;
- papers comparing the use of corticosteroids or not in regimens containing different combinations of antituberculosis drugs;
- papers considering the use of corticosteroids in regimens for drug susceptible TB that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol);
- papers considering the use of drugs not licensed in the UK;
- observational studies, case series, case studies and narrative reviews.

The literature search produced a database of 1768 abstracts. 160 full-text articles were ordered, and 27 papers describing 24 primary studies met the inclusion criteria. These included 4 studies for pulmonary TB, 5 studies for pleural TB, 1 study for TB-associated bronchial obstruction, 8 studies reported in 10 papers for central nervous system TB, 1 study for bone and joint TB (including spinal TB), 4 studies reported in 5 papers for pericardial TB and 1 study for TB-associated immune reconstitution inflammatory syndrome.

Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used Review Manager to meta-analyse the data into pooled effect estimates. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E). There was sufficient data available for a number of sites to allow subgroup analyses to be conducted for children, people with HIV and for people with different severity of disease.

4.7.4 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 697 records were returned. After a title and abstract sift, no records were found that matched the inclusion

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criteria.

4.7.52 Evidence statements

Pleural tuberculosis

Very low quality evidence from 2 randomised controlled trials of 40 and 117 patients comparing antituberculosis chemotherapy plus prednisolone against antituberculosis chemotherapy placebo was inconclusive about which was the most effective in terms of improving the signs and symptoms of disease – including the disappearance of fever, chest pain, shortness of breath and effusion, as well as the incidence of pleural thickening and adhesions – in patients with active pleural TB, although the direction of effect generally favoured prednisolone.

Very low quality evidence from 1 non-randomised controlled trial of 50 patients comparing antituberculosis chemotherapy plus dexamethasone against antituberculosis chemotherapy alone was inconclusive about which was the most effective in terms of improving the signs and symptoms of disease – including changes in weight and the time to clearance of fever, cough, chest pain, shortness of breath and effusion – in patients with active pleural TB, although the direction of effect consistently favoured dexamethasone.

Low to moderate quality evidence from 1 randomised controlled trial of 197 patients coinfected with HIV comparing antituberculosis chemotherapy plus prednisolone against antituberculosis chemotherapy plus placebo showed prednisolone to be associated with a higher incidence of signs and symptoms of disease (including cough, anorexia and effusion), recurrence and adverse events that required discontinuation of treatment in patients with active pleural TB.

Tuberculosis with severe bronchial obstruction

Very low quality evidence from 1 randomised controlled trial comparing antituberculosis chemotherapy plus prednisolone against antituberculosis chemotherapy alone showed the use of prednisolone to be associated with a higher incidence of radiographic improvement, better bronchoscopy scores, and a reduced need for multiple bronchoscopies.

Central nervous system tuberculosis

Very low quality evidence from a meta-analysis of 7 randomised controlled trials of 1192 patients comparing antituberculosis chemotherapy plus any corticosteroid against antituberculosis chemotherapy alone or plus placebo showed corticosteroids to be associated with a lower incidence of mortality (OR 0.75 (95% CI 0.56 to 0.99)).

Very low quality evidence from a meta-analysis of 2 randomised controlled trials of 339 patients comparing antituberculosis chemotherapy plus any corticosteroid against antituberculosis chemotherapy alone or plus placebo showed corticosteroids to be associated with a lower incidence of neurological abnormalities, although the effect was not statistically significant (OR 0.47 (95% CI 0.21 to 1.04)).

Very low quality evidence from a meta-analysis of 5 randomised controlled trials of 943 patients comparing antituberculosis chemotherapy plus dexamethasone against antituberculosis chemotherapy alone or plus placebo showed dexamethasone to be associated with a lower incidence of mortality, although the effect was not statistically significant (OR 0.79 (95% CI 0.61 to 1.02)).

High quality evidence from 1 randomised controlled trial of 545 patients comparing antituberculosis chemotherapy plus dexamethasone against antituberculosis chemotherapy plus placebo showed dexamethasone to be associated with a lower rate of mortality 0 to 3

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months after randomisation (HR 0.62 (95% CI 0.44 to 0.88)), and with a higher survival rate at years 1 to 3 after treatment initiation, although the effect was only statistically significant at 1 year. Amongst those who had stage 1 disease on admission, the survival rate was significantly higher in the dexamethasone group over the 5-year follow-up, although statistically so for years 1 to 3 only. Additionally, dexamethasone was associated with a lower incidence of severe events causing or threatening to cause prolonged hospital stay, disability or death (OR 0.53 (95% CI 0.31 to 0.88).

Very low quality evidence from a meta-analysis of 2 randomised controlled trials of 200 patients (both adults and children) comparing antituberculosis chemotherapy plus prednisolone against antituberculosis chemotherapy alone or plus placebo was inconclusive about which was the most effective in reducing the incidence of mortality (OR 0.81 (95% CI 0.08 to 8.31)). Evidence from the 2 trials was also inconclusive about which was the most effective in terms of changes in the signs and symptoms of disease and the incidence of recurrence or adverse events. Evidence from the 141 patients in the paediatric trial alone showed prednisolone to be associated with a lower incidence of both mortality (OR 0.27 (95% 0.08 to 0.88)) and tuberculoma (OR 0.20 (95% 0.04 to 0.97)).

Very low quality evidence from 1 randomised controlled trial of 49 patients comparing antituberculosis chemotherapy plus methylprednisolone against antituberculosis chemotherapy plus placebo was inconclusive about which was the most effective in terms of mortality, changes in the signs and symptoms of disease and the incidence of adverse events.

Bone and joint tuberculosis

Very low quality evidence from 1 randomised trials of 16 patients comparing antituberculosis chemotherapy plus prednisolone against antituberculosis chemotherapy alone was inconclusive about which was the most effective in terms of the number of patients who failed to gain weight during treatment and the need for additional surgical intervention due to insufficient response to treatment in people with active bone and joint TB.

Pericardial tuberculosis

Very low quality evidence from a meta-analysis of 4 randomised controlled trials of 473 patients comparing antituberculosis chemotherapy plus prednisolone against antituberculosis chemotherapy plus placebo showed prednisolone to be associated with a lower incidence of mortality, although this effect was not statistically significant (OR 0.70 (95% CI 0.45 to 1.08)).

Other sites of tuberculosis

No studies were identified that met the inclusion criteria.

Tuberculosis-associated immune reconstitution inflammatory syndrome

Very low quality evidence from 1 randomised controlled trial of 110 patients comparing antituberculosis chemotherapy plus prednisolone against antituberculosis chemotherapy plus placebo showed prednisolone to be associated with a greater number of patients demonstrating improvement or resolution of their chest radiographs (OR 3.20 (95% CI 1.44 to 7.09)) and fewer patients showing deterioration on their chest radiographs (OR 0.16 (95% CI 0.05 to 0.52)). However, prednisolone was also associated with a higher incidence of adverse drug reactions (OR 2.95 (95% CI 0.74 to 11.78)) and infections (OR 2.16 (95% CI 0.99 to 4.7)), although these effects were not statistically significant.

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4.7.61 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), changes in the signs and symptoms of TB and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision making. Relapse, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of TB.
Trade-off between benefits and harms	The inflammatory immune response to tuberculosis can potentially lead to tissue damage. This immunopathology contributes to both morbidity and mortality, though the pattern of morbidity and risk of progression to death depends very much on the site of disease and the vigour and extent of the immune response. A relatively small immune response leading to oedema and brain swelling within the brain can be fatal, whereas a vigorous immune response around a lymph node in the neck may lead to unpleasant suppuration and exudation of pus to the skin surface, but is less likely to cause death. Steroids have the potential to reduce the inflammatory response and therefore may mitigate against the adverse effects of the immunopathology. On the other hand, by interfering with the immune response steroids may permit bacilli to continue to multiply, thus slowing or preventing the resolution of the pathology through chemotherapy. There are also concerns that steroids may reduce the effects of antituberculosis drugs, either by interfering with absorption or by pharmacokinetic interactions. In addition, steroids have additional potential effects, reducing the body's own steroid responses from the adrenal glands, osteoporosis, psychosis, upper gastrointestinal ulceration and bleeding, and increasing patients' vulnerability to other bacterial and fungal infections. Given the variation in impact of the inflammatory immune response by site, the GDG considered the evidence for adjunctive corticosteroid use on a site-by-site basis. **Pulmonary tuberculosis** The GDG noted that the data available for the main patient-important outcomes (mortality and relapse) did not show a significant difference between the use of antituberculosis chemotherapy with adjunctive corticosteroids and the use of antituberculosis chemotherapy without. Furthermore, the GDG also noted the lack of evidence to consider concerning the potential harms, such as adverse drug reactions, of using adjunctive corticosteroids. There were, however, some differences noted in a number of measures relating to a patient's radiographic status. Specifically, the use of corticosteroids was associated with increased disappearance or lessening of cavitation, and with greater radiographic improvement more generally. Additionally, adjunctive corticosteroids were associated with a higher number of patients with a marked decrease in bacillary count after 50 days of treatment or achieving sputum conversion after 1 month. The GDG noted that, although these outcomes were not predefined as the most critical to patients, they are indicators of infectiousness and may therefore be important outcomes in infection control. Despite this, the GDG did not feel that the evidence was strong enough to support a recommendation for the use of adjunctive corticosteroids in the treatment of active pulmonary tuberculosis. Although the evidence did not demonstrate a significant benefit or harm, the GDG also felt it was noteworthy that there was insufficient evidence of 'no difference', and that equivalence between the use of antituberculosis chemotherapy with adjunctive corticosteroids and the use of antituberculosis chemotherapy alone was not conclusively demonstrated.

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Pleural tuberculosis

The GDG noted that the use of corticosteroids was generally associated with more patients achieving resolution or clearance of the signs or symptoms of disease, including fever, cough, shortness of breath, weight change, pleural effusion and chest pain, or achieving resolution or clearance within a shorter time period. However, this effect was rarely statistically significant, or the GDG was often unable to assess the significance of this effect due to a lack of data. In patients without HIV or in whom HIV status was not specified, the only additional outcome data available to assist in the GDG's decision-making were the incidence of recurrence and number of patients to experience an adverse event. Neither of these outcomes demonstrated a significant effect.

1 study examined the use of adjunctive corticosteroids in patients coinfected with HIV. This study reported adjunctive corticosteroids to be associated with a higher incidence of cough and anorexia (signs and symptoms of tuberculosis), a higher rate of recurrence and a higher incidence of adverse events. The GDG felt that these effects, graded at low or moderate quality, were noteworthy and that they highlight the need to be careful when using corticosteroids in patients with HIV; however, they did not feel that these effects conclusively demonstrated sufficient harm to warrant a recommendation against the use of adjunctive corticosteroids in this population.

Again, although the evidence rarely demonstrated a significant benefit or harm, the GDG felt it was noteworthy that there was insufficient evidence of 'no difference', and that equivalence between the use of antituberculosis chemotherapy with and without adjunctive corticosteroids was not demonstrated.

The paucity of conclusive evidence meant that the GDG did not feel able to make any recommendation on the use of corticosteroids in patients with pleural tuberculosis.

Tuberculosis with severe bronchial obstruction

The GDG discussed the evidence available for the use of adjunctive corticosteroids in patients with tuberculosis with severe bronchial obstruction and noted both its paucity and the significant limitations in its quality and generalizability (see 'quality of evidence' below). However, even though the study had a small sample size of just 29 patients, the GDG was struck by the significant treatment effects observed. Patients receiving corticosteroids had significantly more improvement in their radiological status and bronchoscopy scores than patients who did not receive corticosteroids, and also required fewer bronchoscopies.

Despite these encouraging results, the paucity of evidence meant that the GDG did not feel able to make any recommendation on the use of corticosteroids in patients with tuberculosis-associated bronchial obstruction.

Central nervous system tuberculosis

The GDG discussed the evidence identified for the adjunctive use of corticosteroids in patients with central nervous system tuberculosis and noted that, for many of the outcomes analysed, the difference in treatment effects between those who received corticosteroids and those who did not was not significant. However, the use of corticosteroids did appear to lower the incidence of mortality, neurological abnormalities and events causing prolonged hospital stays or disability.

The GDG also considered the use of corticosteroids at different stages of the disease. These subgroups consisted of relatively small samples so the effect estimates did not reach statistical significance. Despite this, across all severities of disease the direction of effect consistently favoured corticosteroid use, with more advanced stages of disease demonstrating the strongest effect.

When the GDG considered the different corticosteroids individually, they noted that dexamethasone significantly lowered the incidence of residual neurological abnormalities and events causing prolonged hospital stays, disability or death, as well as the incidence of mortality, although this latter effect was not statistically

significant. The only outcome for which prednisolone achieved a significant effect was in the lowering of the incidence of mortality and tuberculoma in children. However, the study populations in the prednisolone trials were relatively small, which may explain their failure to detect significant treatment effects.

When the GDG considered the relative effectiveness of the different corticosteroids, they noted that, although dexamethasone did not perform substantially better than prednisolone in the subgroup analyses, there were more positive results and more evidence generally available for its use. Additionally, the GDG noted that dexamethasone is known to be more readily absorbed than prednisolone, meaning that it has an earlier onset of action, and that this rapidity is desirable given the speed and severity of the effects of this form of tuberculosis. However, evidence for the use of dexamethasone explicitly in children was lacking. The GDG felt that the evidence available for methylprednisolone was inconclusive, despite the anticipation that methylprednisolone is a more potent corticosteroid and the fact large doses were given.

Despite these observations, the GDG did not feel they could make a strong recommendation about which corticosteroid in which dosing regimen should be used for patients with central nervous system tuberculosis. Standard practice for the dosing of drugs in recommendations would be to refer clinicians to the British National Formulary (BNF); however, the GDG noted that the BNF does not currently contain appropriate guidance on the dosing of corticosteroids for patients with central nervous system tuberculosis, with recommended doses considerably lower than those being effectively used in the evidence reviewed and in their clinical experience. They also felt that the doses recommended in the previous NICE guideline were too low. Therefore, although unwilling to be overly prescriptive due to the variability of regimens within the evidence, the GDG concluded that example regimens should be provided within the recommendation to guide clinicians in their prescribing.

In the case of adults, the GDG felt that the key study, given the sample size, length of follow-up and the overall quality of the outcome data, as well as the beneficial effects observed, was the Vietnamese RCT, and therefore the regimens of dexamethasone, prescribed according to the severity of disease, were cited as an exemplar. Although this trial consisted predominantly of adults (defined within this guideline as those over 18 years of age), there were a number of children included in the study population. The GDG felt that this should be noted, but they did not feel that the small number of 15 to 18 year olds was of sufficient concern (either in their impact on the treatment effects observed, nor on the underlying design of the regimen in the first place) to not use the regimen prescribed.

In the case of children, the only explicitly paediatric evidence examining the use of corticosteroids used prednisolone. Since this study showed prednisolone to be associated with significantly lower incidences of mortality and tuberculoma, the GDG felt that the regimen used in this study would be an appropriate example of a paediatric regimen. The GDG also felt that, where possible, corticosteroid regimens for children should be administered orally because intramuscular or intravenous administration is particularly difficult, as well as painful and unpleasant for the child.

A gradual withdrawal of the corticosteroids was recommended over 4 to 8 weeks, with patients with more advanced disease receiving the longer durations of treatment. This reflected the durations used in the evidence base, as well as treatment periods deemed effective by the GDG in their own clinical experience. Gradual withdrawal was also considered to be a key element of the regimen design, as sudden withdrawal of corticosteroids is known to be associated with adverse withdrawal reactions.

Bone and joint tuberculosis

The GDG discussed the evidence available for the use of adjunctive corticosteroids in patients with bone and joint, including spinal, tuberculosis and concluded that the small, single study of just 16 patients was not useful to their decision-making. It provided data for only 2 outcomes of interest, the need for additional surgical intervention (taken as an indicator of a patients' response to

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treatment) and the number of patients who failed to gain weight, of which neither demonstrated a significant effect.

The GDG reflected on the possible reasons for using corticosteroids in patients with bone and joint tuberculosis and felt that there may be a role for corticosteroids in preventing the loss of cartilage through inflammatory tissue damage, although did not feel that this presented a strong enough indication to recommend their use. They also felt that they may have had a role in ensuring bone penetration of the antituberculosis drugs, although the advent of rifampicin (the single paper identified predates the availability of rifampicin), which penetrates bone effectively without the use of corticosteroids, has removed this potential indication.

Pericardial tuberculosis

The GDG noted that there was some evidence to show that corticosteroids decreased mortality, although this effect was not statistically significant.

Evidence was available for pericardial tuberculosis of different stages – 3 RCTs in patients with effusive pericardial tuberculosis, and 1 RCT in patients with constrictive tuberculous pericarditis, a more advanced stage of disease. The GDG noted that, in their experience, the use of corticosteroids is more about preventing constrictive pericarditis in patients with effusive disease, in whom the advancement of the disease can lead to fibrosis and then to constrictive pericarditis, than it is about treating constrictive pericarditis once it has developed. Therefore, they felt that the clinical benefit of corticosteroids would likely be greater in patients with effusive pericardial tuberculosis rather than constrictive tuberculous pericarditis.

Overall, the GDG felt that the evidence supported the use of corticosteroids in patients with pericardial tuberculosis. Although the meta-analysis did not provide strong evidence in terms of corticosteroid use reducing mortality, this meta-analysis was unable to include the longterm survival data from the Strang paper due to the format in which it was reported. When viewed in isolation, the survival analysis in this paper showed a clear protective effect.

The group felt that the doses of corticosteroid previously recommended were still appropriate, as was a a gradual withdrawal of the corticosteroids. The GDG considered this to be a key element of the regimen design, as sudden withdrawal of corticosteroids is known to be associated with adverse withdrawal reactions.

The GDG also felt that, where possible, corticosteroid regimens for children should be administered orally because intramuscular or intravenous administration is particularly difficult, as well as painful and unpleasant for the child.

Other sites of tuberculosis

No evidence was found for other sites of tuberculosis, including peripheral lymph node, gastrointestinal, genitourinary and disseminated tuberculosis. The GDG discussed their own experiences of the use of corticosteroids in these types of tuberculosis, and although they acknowledged that they are currently prescribed by some clinicians, particularly for genitourinary and abdominal tuberculosis, they did not feel able to make any recommendations on their use without evidence from clinical trials.

Tuberculosis-associated immune reconstitution inflammatory syndrome

The GDG discussed the evidence available for the use of adjunctive corticosteroids in patients with tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) and noted their association with a better radiographic status and, although not statistically significant, with greater improvement in patients' symptoms. However, they also noted their association with a higher incidence of adverse drug reactions and secondary infections, although this association was not statistically significant either.

The GDG did not feel they had sufficient evidence from which to make a recommendation regarding the use of corticosteroids for TB-IRIS, although they also noted that this may have been due to the fact that the literature search had not been specifically designed to detect such papers. The GDG highlighted the

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	importance of this topic, also noting that future decisions regarding the use of corticosteroids for TB-IRIS should be based upon a targeted systematic review of the area.
Trade-off between net health benefits and resource use	Owing to the poor quality and quantity of clinical evidence, and the fact that no health economic evidence was returned from the searches for these questions, the GDG was unable to consider in detail whether there would be any trade-offs between net health benefits and resource use. Prescribing corticosteroid medications is unlikely to have a significant impact on resources, as the medicines are available in generic formulations.
Quality of evidence	There was also some pooling of studies by site of disease, although these often had a number of limitations. In addition to a lack of relevant trials, the evidence base suffered from the presence of significant heterogeneity, including variations in the age and HIV status of the populations, and of the corticosteroid and antituberculosis regimens across the studies. Furthermore, a number of the antituberculosis regimens did not use all of, or only, the standard regimen of drugs, as recommended by NICE, nor did they consistently use the recommended durations of treatment. The standard regimen consists of 4 drugs: isoniazid and rifampicin for the full treatment period, supplemented by pyrazinamide and ethambutol for the first 2 months of treatment. It is recommended that this regimen is given for a total 6 months to patients with no central nervous system (CNS) involvement in their disease or 12 months to those who do have CNS involvement. Deviation of the regimens under examination from this framework limited the applicability of the evidence to UK practice. Of particular concern were the regimens that lacked rifampicin, since this drug is now widely considered to be a critical component of a successful regimen. These issues were reflected in the appraisal of the quality of the evidence for each outcome. **Pulmonary tuberculosis** No paediatric evidence was identified. There was a paucity of data on outcomes of interest, with the GDG noting the lack of data on the potential harms of using adjunctive corticosteroids in particular. There was also a lack of data available for cure, treatment success and failure, and adherence to treatment. Furthermore, the GDG highlighted an absence of evidence on the impact of corticosteroids on the ‘functionality’ of patients. The use of corticosteroids is currently undertaken with the intention of reducing the restrictions upon patients’ future ability to function (in the case of pulmonary tuberculosis, this generally refers to pulmonary function); that is, to ensure that people can live their lives without severe functional restriction resulting from permanent tissue damage. Therefore the GDG felt that information concerning the impact of corticosteroids on long-term pulmonary function and patient quality of life would be useful to future decision-making. No evidence was found for the impact of corticosteroids on cure or treatment failure in patients with active pulmonary tuberculosis. The quality of evidence across the outcomes that were available was ‘very low’. The antituberculosis regimens employed in the studies did not always use all of or just the 4 standard recommended drugs. In 1 paper, the regimens used either did not use rifampicin throughout the whole treatment period, or did not use rifampicin at all. This deviation from the standard regimen was particularly concerning as the use of rifampicin is now considered to be essential to a successful therapeutic regimen. Such deviations from the standard recommended regimen make the evidence less directly applicable to UK practice. Furthermore, the different antituberculosis regimens used across the studies may have introduced heterogeneity into the meta-analyses conducted. Additionally, a number of substitute outcomes were extracted by the reviewer, grouped under the label of 'response to treatment'. ‘Response to treatment', or more specifically the number of patients to achieve sputum conversion or experience a decrease in their bacillary count, was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure,

although it was not an outcome pre-specified as a patient-important outcome and was therefore downgraded for indirectness.

The GDG also noted that one of the studies, the Turkish study, explicitly examined the use of corticosteroids in patients with advanced disease. In patients with advanced disease, corticosteroids may have been given for reasons other than the 'usual' (that is, the prevention of tissue damage that can result from an inflammatory response to the disease), such as steroid replacement. This further limits the generalisability of this evidence to pulmonary tuberculosis more widely.

Reporting was often poor, with limited information available regarding study design (including method of randomisation, and the use of allocation concealment and blinding), the comparability of intervention and comparator groups (both at baseline and in terms of the availability of data) and details of the antituberculosis regimens used (including doses, frequency of dosing and duration of treatment).

Pleural tuberculosis

No paediatric evidence was identified.

There was a paucity of data on outcomes of interest, including a lack of data available for cure, treatment success and failure, and adherence to treatment.

Again, the antituberculosis regimens employed in the studies did not always use all of or just the 4 standard recommended drugs. In 1 paper, the only study to examine the use of dexamethasone in patients with pleural tuberculosis, the regimen did not contain rifampicin. As previously stated, this deviation from the standard regimen was particularly concerning as the use of rifampicin is now considered to be essential to a successful therapeutic regimen, and such deviations from the standard recommended regimen make the evidence less directly applicable to UK practice.

Additionally, a number of substitute outcomes were extracted by the reviewer, including 'response to treatment' and 'recurrence'. 'Response to treatment' was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure, although the exact focus of the outcome definitions used varied widely and often also incorporated changes in the signs and symptoms of disease. 'Recurrence' was considered to be a substitute for relapse. Although potentially useful in the absence of data for 'true' relapse, data on recurrence can be difficult to interpret as its definition generally does not distinguish between recurrence of the disease due to relapse and recurrence of the disease due to reinfection.

1 study – the dexamethasone study – was a non-randomised controlled trial that did not use blinding.

There was a significant lack of methodological detail in many of the papers, including a lack of information about the method of randomisation used, or whether or not allocation concealment and blinding were used. This means that the risk of bias in the trials is difficult to appraise, and the quality of evidence was downgraded. Reporting of the comparability of intervention and comparator groups was also poor in terms of details of baseline characteristics and the care received by the 2 groups other than the intervention and comparator, as well as the availability of data during follow-up. Additionally, details provided of the antituberculosis regimens used were also limited in some papers, including the doses, frequency of dosing and duration of treatment prescribed. Furthermore, where continuous variables were reported, standard deviations/errors were rarely given, making the precision of the effect estimates difficult to assess.

The GDG also felt unable to discern between study populations that were comprised largely of new, primary cases of tuberculosis and study populations consisting largely of 'older', persistent or reactivation cases. The group felt that the benefits and harms associated with the use of corticosteroids may be different in these 2 groups of patients, and that further information – particularly on the second group, who are more common in the UK – would be useful to future decision-making.

Tuberculosis with severe bronchial obstruction

Only 1 paper was included, which examined the used of corticosteroids in children. It is not clear if this population contained people with HIV, people without HIV or a combination of 2.

No adult evidence met the inclusion criteria, and the GDG did not feel that the paediatric evidence identified could be generalised to the adult population.

No evidence was found for the impact of corticosteroids on mortality, cure, treatment failure or relapse in patients with tuberculosis-associated bronchial obstruction.

Additionally, the sample size was very small, with just 29 people included. Although the GDG was concerned about how generalisable such a small population would be, they also noted that the small number of participants meant that the significant results observed in favour of the use of adjunctive corticosteroids were particularly noteworthy.

The paper was randomised using a reliable method but the trial was open label, with only the examination of bronchoscopy and radiographs being blinded.

There was a significant lack of methodological detail in the paper, including a lack of information about the use of allocation concealment and about the care the patients received other than intervention and comparator. Additionally, the site of disease was not clearly stated in the paper, with the inclusion criteria specifying only that the patients were being 'treated for symptomatic tuberculosis with severe bronchial obstruction suspected by radiology and demonstrated by bronchoscopy'. Given this description of the locality of the tuberculous lesions, which does not appear to suggest direct airway disease, as well as the young age of the study population (ranging from 4 months to 15 years), the GDG felt it likely that this was tuberculous lymphadenopathy of the mediastinal or hilar lymph nodes.

Central nervous system tuberculosis

All evidence was for meningeal tuberculosis; no evidence was found for other types of central nervous system tuberculosis.

No evidence was found for the impact of corticosteroids on cure or treatment failure in patients with active central nervous system tuberculosis.

Only 1 paediatric trial was identified, which examined the use of prednisolone. No evidence was identified that explicitly examined the use of dexamethasone in children, although approximately 60% of the population in the Egyptian RCT were under the age of 15. In addition to this, a proportion of children were involved in a number of other trials. Whilst it is positive that children were involved to some degree in the evidence base, the GDG noted that there is also the disadvantage that adults' and children's' clinical presentation of central nervous system tuberculosis is often different, and that the paediatric cohort in the predominantly adult populations may be skewing the treatment effects. Further studies in children would be particularly desirable, but so too would studies examining the use of corticosteroids exclusively in adults.

Due to the different approaches of structuring regimens, with different initial doses, different periods over which the drugs were gradually withdrawn and different metrics in which the doses were reported, the corticosteroid dosing regimens used in the studies were not always straightforward to interpret. It was therefore difficult to compare the effectiveness of different corticosteroids or regimens across studies, although approximations of the equivalent doses used of each drug in the included studies suggested that the doses of dexamethasone used may have been higher than those for prednisolone. The GDG emphasized the need for more and clearer data to allow an analysis of the safest and most effective dosing regimens for each corticosteroid.

The antituberculosis regimens employed in the studies did not always use all of or just the 4 standard recommended drugs, nor were any of the regimens given for the 12-month period currently recommended. Where details of the regimens were given, all studies gave antituberculosis drugs for just 6 or 9 months, except for the 2 Egyptian RCTs, both of which gave antituberculosis drugs for 24 months but neither of which used rifampicin. These deviations from the recommended regimen make the evidence less directly applicable to UK practice. Additionally,

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the GDG felt that these inadequate antituberculosis regimens may have caused the high rates of severe events, such as mortality and relapse, seen in many of the studies.

Additionally, a number of substitute outcomes were extracted by the reviewer. The first group, aggregated under the label of 'response to treatment' and including the extent of recovery and the need for additional intervention, was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure, although it was not an outcome pre-specified as a patient-important outcome and was therefore downgraded for indirectness. The other substitute outcome, 'recurrence', was considered to be a substitute for relapse. Although potentially useful in the absence of data for 'true' relapse, data on recurrence can be difficult to interpret as its definition generally does not distinguish between recurrence of the disease due to relapse and recurrence of the disease due to reinfection.

Follow-up varied widely across the studies, from 3 months to 5 years. This variation may have introduced heterogeneity into the meta-analyses conducted for mortality.

1 of the Egyptian studies, examining the use of dexamethasone, was not randomised and therefore was not pooled with the RCT data.

There was a significant lack of methodological detail in many of the papers, including a lack of information about the method of randomisation used, or whether or not allocation concealment and blinding were used. This means that the risk of bias in the trials is difficult to appraise, and the quality of evidence was downgraded. Reporting of the comparability of intervention and comparator groups was also poor in terms of details of baseline characteristics and the care received by the 2 groups other than the intervention and comparator, as well as the availability of data during follow-up. Additionally, details provided of the antituberculosis regimens used were also limited in some papers, including the doses, frequency of dosing and duration of treatment prescribed. Furthermore, where continuous variables were reported, standard deviations/errors were rarely given, making the precision of the effect estimates difficult to assess.

Bone and joint tuberculosis

Only 1 study was included, which provided data for just 2 outcomes of interest. The quality of evidence for these outcomes was 'very low'.

No evidence was found for the impact of corticosteroids on mortality, cure, treatment failure or relapse in patients with active bone and joint tuberculosis.

The sample size was very small, with just 16 people included, reducing the sensitivity of the study to detect differences in the treatment effects observed. This is the likely cause of the wide confidence intervals around the odds ratios calculated by the reviewer.

The antituberculosis regimen employed did use all of or just the 4 standard recommended drugs: just streptomycin and isoniazid were used. As previously stated, a deviation from the standard regimen of this type was particularly concerning as the use of rifampicin is now considered to be essential to a successful therapeutic regimen, and such deviations from the standard recommended regimen make the evidence less directly applicable to UK practice.

Although 'response to treatment', or more specifically the number of patients to require additional surgical intervention, was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure, it was not an outcome pre-specified as a patient-important outcome and was therefore downgraded for indirectness.

In addition to these issues, there was a significant lack of methodological detail, including a lack of information about the method of randomisation used, whether or not allocation concealment and blinding were used, and the duration for which antituberculosis chemotherapy was given. Additionally, the information regarding the comparability of patients at baseline was limited, with only the sites of disease described: 7 patients in the prednisolone group had tuberculosis in the spine, 2 in the knee and 1 in the hip, whereas no patients who received antituberculosis

chemotherapy alone had tuberculosis in the spine, 4 had tuberculosis in the hip and 2 in the knee. The distribution of spinal tuberculosis was not balanced across the 2 groups.

Pericardial tuberculosis

No paediatric evidence available.

No evidence was found for the impact of corticosteroids on cure, treatment failure, relapse or adverse events in patients with active pericardial tuberculosis.

2 of the studies conducted in South Africa were quasi-randomised, with allocation occurring by the consecutive entering of names into a register. This method of randomisation raises concerns over the internal validity, and therefore the risk of bias.

Follow-up varied widely across the 4 studies, from 1 to 10 years. This variation may have introduced heterogeneity into the meta-analyses conducted for mortality.

Again, the antituberculosis regimens employed in the studies did not always use all of or just the 4 standard recommended drugs. Such deviations from the standard recommended regimen make the evidence less directly applicable to UK practice. Furthermore, the different antituberculosis regimens used across the studies may have introduced further heterogeneity into the meta-analyses conducted for mortality.

Additionally, a number of substitute outcomes were extracted by the reviewer, grouped under the label of 'response to treatment'. ‘Response to treatment', or more specifically the number of patients with a ‘favourable’ response to treatment or the number of patients to require surgical intervention, was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure, although it was not an outcome pre-specified as a patient-important outcome and was therefore downgraded for indirectness.

Reporting was poor in some areas, including a lack of information about whether or not allocation concealment was used, as well as the comparability of intervention and comparator groups in terms of details of baseline characteristics and the availability of data during follow-up.

Other sites of tuberculosis

No evidence was found for other sites of tuberculosis, including peripheral lymph node, gastrointestinal, genitourinary and disseminated tuberculosis.

Tuberculosis-associated immune reconstitution inflammatory syndrome

No paediatric evidence available.

No evidence was found for the impact of corticosteroids on cure, treatment failure or relapse in patients with active pericardial tuberculosis.

Although not explicitly stated, all patients were appeared to receive antiretroviral therapy and therefore the assumption was made that the population were all HIV-positive. If this assumption is correct, no data was found for patients without HIV.

Only 1 study was identified from the literature search, although it was felt that this was because the literature search had not been explicitly designed to identify papers relating to TB-IRIS.

Groups were not comparable at baseline in that there was a longer period (p = 0.02) between taking antituberculosis chemotherapy and initiating ART amongst patients in the prednisolone arm (66 days) than the placebo arm (43.5 days), although the impact of this upon the observed treatment effects is unclear.

Patients in either arm of the trial were permitted to transfer to open label prednisolone if they experienced significant clinical deterioration after 2 weeks of follow-up. 15 of 55 patients in the prednisolone transferred to open label prednisolone (that is, they were unblended) and 20 patients in the placebo arm transferred to open label prednisolone. This may have ‘contaminated’ the intent-to-treat analysis of the data. However, the transfer of patients from placebo to prednisolone would be expected to temper the true difference between the 2 arms,

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	therefore this potential confounding does not theoretically change the conclusion that corticosteroids are associated with a better radiographic status and with greater improvement in patients' symptoms. The GDG was also concerned with the small sample size used, which is likely to have reduced the sensitivity of the study to detect statistically significant differences between the treatment arms. The small number of events and wide confidence intervals reported for a number of outcomes support the suggestion that the study were underpowered. In addition to this, there was a lack of methodological detail, including a lack of information about the use of allocation concealment, and the duration for which antituberculosis chemotherapy was given.
Other considerations	None.

4.7.71 Recommendations

Central nervous system TB

68. At the start of an anti-TB treatment regimen, offer people with active TB of the central nervous system dexamethasone or prednisolone, initially at a high dose with gradual withdrawal over 4–8 weeks. An example of a suitable regimen is listed in table 12.

Table 12 Example of suitable corticosteroid regimen for adults

	Stage	
Dose of dexamethasone by week	**1**	**2 or 3**
1	0.3 mg/kg/day (IV)	0.4 mg/kg/day (IV)
2	0.2 mg/kg/day (IV)	0.3 mg/kg/day (IV)
3	0.1 mg/kg/day (oral)	0.2 mg/kg/day (IV)
4	3 mg/day (oral)	0.1 mg/kg/day (IV)
5	2 mg/day (oral)	4 mg/day (oral)
6	1 mg/day (oral)	3 mg/day (oral)
7	–	2 mg/day (oral)
8	–	1 mg/day (oral)
Abbreviation: IV, intravenous		

[new 2015]

69. At the start of an anti-TB treatment regimen, offer children and young people with active TB of the central nervous system dexamethasone or prednisolone. This should initially be at a high dose with gradual withdrawal over 4–8 weeks. An example of a suitable regimen is oral prednisolone, starting at a dose of 4 mg/kg of body weight/day. [new 2015]

Pericardial TB

70. In adults with active pericardial TB, offer oral prednisolone at a starting dose of 60 mg/day, gradually withdrawing it 2–3 weeks after starting treatment. [2015]

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71. In children and young people with active pericardial TB, offer oral prednisolone at a starting dose of 1 mg/kg of body weight/day (maximum 40 mg/day), gradually withdrawing it 2–3 weeks after starting treatment. [2015]

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4.8 Use of adjunctive surgery in people with active tuberculosis

4.8.1 Clinical introduction

This evidence review focused on the use of adjunctive surgery in people with active tuberculosis who are receiving antituberculosis chemotherapy. Therapeutic surgical interventions can be broadly grouped into 2 categories:

- surgery for the removal of diseased tissue, with the aim of increasing the likelihood of achieving cure; and
- surgery for the management of the signs and symptoms of tuberculosis, with the aim of reducing related mortality and long-term morbidity.

In addition to this, surgery is sometimes used to collect tissue for diagnostic assessment.

4.8.2 Review question

In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), does surgery as an adjunct to an antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

4.8.3 Evidence review

For this review question, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the use of adjunctive surgery in people with active tuberculosis who are receiving antituberculosis chemotherapy. Randomised, quasi-randomised and non-randomised controlled trials were considered for inclusion, as were cohort studies, case-control studies and case series. Papers of interest were those that compared the use of antituberculosis chemotherapy plus adjunctive surgery to antituberculosis chemotherapy alone. (See appendix C for the full review protocol).

Trials were excluded if:

- the population included people with latent TB;
- the population included people undergoing surgery in the absence of antituberculosis chemotherapy;
- the paper focused primarily on populations with comorbidities or coexisting conditions (other than HIV) that will affect the choice or management of treatment;
- papers using regimens for drug susceptible TB that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol);
- papers considering the use of drugs not licensed in the UK; or
- case studies or narrative reviews.

From a database of 2199 abstracts, 391 full-text articles were ordered and 36 papers describing 33 primary studies met the inclusion criteria. The types of intervention studied included:

- spinal TB: radical Hong Kong surgery, costotransversectomy surgery, debridement or laminectomy and spinal fusion, decompression or stabilisation, abscess drainage,

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thoracotomy, vertebrectomy, transpedicular decompression, retroperitoneal approach, posterior instrumentation and/or graft

- CNS TB: all 4 studies investigated shunt surgery
- bone and joint TB: synovectomy and debridement, curettage, or curettage and arthrodesis
- genitourinary TB: both ablative and reconstructive surgery
- pulmonary TB: ranged from resection of 1 segment, to resection of 2 or more segments, lobectomy, extended lobectomy and total pulmonectomy
- endobronchial TB: argon plasma coagulation
- chest wall: surgical intervention ranged from simple incision and drainage to extensive debridement of regional soft tissues and underlying ribs or cartilages
- DR-TB: surgical resection to remove diseased or destroyed tissue

Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used Review Manager to meta-analyse the data into pooled effect estimates. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

4.8.4 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 2199 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

4.8.5 Evidence statements

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Use of adjunctive surgery in people with active, drug susceptible spinal tuberculosis

Very low quality evidence 1 randomised controlled trial of 304 patients showed the use of adjunctive surgery in patients with active, drug susceptible spinal tuberculosis to be associated with a higher incidence of mortality than the use of antituberculosis chemotherapy alone, although it was inconclusive about which was the most effective in terms of changes in the signs and symptoms of disease, including bony fusion, kyphosis, vertebral loss, myelopathy, sinuses and abscesses.

Very low quality evidence 1 non-randomised controlled trial of 33 patients was inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of the incidence of relapse and changes in the signs and symptoms of disease, including impairment of motor function and physical activity, myelopathy, sinuses and abscesses.

Very low quality evidence from 4 observational studies and 5 case series were inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of the incidence of mortality and relapse, as well as changes in the signs and symptoms of disease, including neurological deficit, pain, bony fusion, kyphosis, sinuses and abscesses.

Use of adjunctive surgery in people with active, drug susceptible central nervous system tuberculosis

Very low quality evidence from 1 case-control study of 56 children, matched for age and severity of disease, showed the use of adjunctive shunt surgery in patients with active, drug susceptible tuberculous meningitis and hydrocephalus to be associated with associated with a lower incidence of mortality and a higher incidence of being defined as ‘well’.

Very low quality evidence from 3 observational studies (2 prospective and 1 retrospective) of 65, 49 and 387 patients, respectively, showed the use of adjunctive shunt surgery to be associated with a higher incidence of neurological deficit or death in people with active, drug susceptible tuberculous meningitis and hydrocephalus.

Use of adjunctive surgery in people with active, drug susceptible bone and joint tuberculosis

Very low quality evidence from 1 retrospective observational study of 30 patients and 1 case series of 16 patients was inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of changes in the signs and symptoms of disease, including bony fusion and deformity, and in terms of the recurrence of disease.

Use of adjunctive surgery in people with active, drug susceptible genitourinary tuberculosis

Very low quality evidence from 2 observational studies (1 prospective and 1 retrospective) of 77 and 92 patients, respectively, was inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of the incidence of treatment failure, the incidence of treatment default and the need for additional intervention in people with active, drug susceptible genitourinary tuberculosis.

Use of adjunctive surgery in people with active, drug susceptible pulmonary tuberculosis

Very low quality evidence from 1 retrospective observational study of 232 patients showed the use of adjunctive surgery to be associated with a higher incidence of cure and a lower incidence of treatment failure in people with active, drug susceptible pulmonary tuberculosis; despite this, the study was inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of reducing mortality.

Use of adjunctive surgery in people with active, drug susceptible endobronchial tuberculosis

Very low quality evidence from 1 retrospective observational study of 115 patients was inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of the improvement, deterioration or recurrence of endobronchial lesions in people with tumorous, drug susceptible endobronchial tuberculosis without bronchial stenosis.

Use of adjunctive surgery in people with active, drug susceptible chest wall tuberculosis

Very low quality evidence from 1 case series of 7 patients was inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of achieving a ‘good outcome’ in people with active, drug susceptible tuberculosis of the chest wall.

Use of adjunctive surgery in people with active, drug resistant tuberculosis

Very low quality evidence from 6 cohort studies (1 prospective and 5 retrospective), observing a total of 2322 patients with multidrug-resistant tuberculosis, was inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of reducing mortality.

Very low quality evidence from 2 cohort studies (1 prospective and 1 retrospective), observing a total of 297 patients with multidrug-resistant tuberculosis, showed the use of adjunctive surgery to be associated with a higher incidence of cure than the use of antituberculosis chemotherapy alone; very low quality evidence from 2 other cohort studies (both retrospective), observing a total of 456 patients with multidrug-resistant tuberculosis, were inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of cure.

Very low quality evidence from 1 retrospective cohort study of 162 patients with multidrug-resistant tuberculosis showed the use of adjunctive surgery to be associated with a lower incidence of treatment failure than the use of antituberculosis chemotherapy alone; very low quality evidence from 4 other cohort studies (1 prospective, 3 retrospective), observing a total of 753 patients with multidrug-resistant tuberculosis, were inconclusive about whether the use of surgery in addition to antituberculosis chemotherapy was more effective than antituberculosis chemotherapy alone in terms of reducing the incidence of treatment failure.

4.8.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), relapse and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment, as well as post-operative complications, were critical for decision-making. Changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of TB. 'Recurrence' was also not a predefined outcome of interest, though it was considered a potentially useful substitute for relapse.
Trade-off between benefits and harms	**Drug susceptible, spinal tuberculosis:** The GDG noted that there was some evidence to suggest that the use of adjunctive surgery may be beneficial in patients with active, drug susceptible spinal tuberculosis: the randomised controlled trial showed surgery to be associated with a significantly lower incidence of tuberculosis-related mortality, as well as a lower incidence of deterioration in vertebral loss, although this effect was not statistically significant. Additionally, evidence from the included observational studies suggested that the use of adjunctive surgery may be associated with improved signs and symptoms of disease, including spinal fusion, kyphosis and neurological status. Despite this, the GDG did not feel that there was strong evidence either for or against the use of surgery, nor did they feel able to give detailed recommendations relating to the type of surgery that should be used. The group therefore recommended that surgery should not be routinely performed in patients with drug susceptible spinal tuberculosis, and that the decision to undergo surgery should be taken on a case-by-case basis by a specialist with experience in managing these patients, both surgically and nonsurgically. Additionally, given that all surgeries in the included evidence were performed in response to spinal instability or compression, the group felt that it was only these patients who should be considered for surgical intervention. The risks associated with spinal surgery can be very severe – including both death and disability – and the group emphasised the need to make sure that patients are fully informed of the risks, as well as the possible benefits, to their future quality of life. **Drug susceptible, central nervous system tuberculosis:** The GDG noted that the use of shunt surgery was associated with a higher incidence of neurological deficit or death in the included cohort studies; however, they felt that the usefulness of this evidence to their decision-making

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was limited by the fact that allocation to receive shunt was based on confounding factors. Specifically, it was felt that this data reflects the fact that these patients had more severe disease than those who did not undergo shunt surgery, rather than the true treatment effect.

Only 1 paper, the case-control study, attempted to balance the groups by severity of disease; this paper showed surgery to be associated with a lower incidence of mortality and a higher incidence of being defined as 'well' (or having only a minor physical abnormality which did not interfere with his or her lifestyle). Despite this, the group did not feel that this constituted a sufficiently strong evidence base, given the small size of the study (n = 56) and poor quality of the evidence, from which to make a recommendation about the use of shunt surgery in patient with drug susceptible tuberculous meningitis and associated hydrocephalus.

The group did, however, note that in their experience delays to the use of shunt surgery in patients with severe hydrocephalus can lead to unnecessary deaths. They felt that this can be a particular issue in patients with TB or TB-HIV coinfection as the health professionals involved in the patient's care may be concerned about infectiousness. The group felt that, whilst it is important to avoid unnecessary surgery, it is important to encourage clinicians to act swiftly when there is evidence of raised intracranial pressure. Further to this, the group felt it was important to state that they did not wish to discourage the appropriate use of diagnostic surgery.

Drug susceptible, bone and joint tuberculosis:

The group felt that the included studies provided little evidence either for or against the use of surgery for drug susceptible bone and joint tuberculosis, and that there was too much variation (with regard to population studied and surgical intervention used) to allow them to make a recommendation. The decision to undergo surgery should be taken on a case-by-case basis.

The group felt that the appropriate use of diagnostic surgery for bone and joint tuberculosis should not be discouraged. They also noted that the risks associated with surgery for bone and joint tuberculosis were, in their experience, relatively moderate, with severe events such as surgery-related death being comparatively uncommon.

Drug susceptible, genitourinary tuberculosis:

The group felt that the included studies provided little evidence either for or against the use of surgery in patients with drug susceptible genitourinary tuberculosis. Whilst the complication rates are low, the lack of evidence for a benefit from surgery meant that any complications would be unacceptable.

Drug susceptible, pulmonary tuberculosis:

The single study identified showed the use of surgery to be associated with higher incidence of cure and a lower incidence of treatment failure than the use of antituberculosis chemotherapy alone. Though rare in current practice, the GDG noted that there could be a role for surgery when there is extensive cavitation, poor blood supply and poor penetration of antituberculosis drugs; however, the group felt that where appropriate antituberculosis drug regimens are used, surgery is not necessary to achieve cure, particularly given the high rates of complications and their severe consequences.

Drug susceptible, endobronchial tuberculosis:

A single retrospective study was identified; it was felt that this provided little evidence either for or against the use of surgery in patients with drug susceptible endobronchial tuberculosis.

Drug susceptible, chest wall tuberculosis:

The available evidence was inconclusive about the balance of benefits and

	harms associated with the adjunctive use of surgery, with no significant effect observed with regards to achieving a 'good outcome' (no clear definition provided). **Drug resistant tuberculosis:** The GDG noted that there was some evidence to suggest that the use of adjunctive surgery may be associated with a higher incidence of cure and a lower incidence of treatment failure in patients with multidrug-resistant tuberculosis. However, the group also noted this benefit did not seem to translate into improved mortality rates. Furthermore, the group could not be confident that the benefits observed were free from bias, given the potentially confounding criteria used to select those patients who were to undergo surgery in many of the studies. These included extensive drug resistance, a high chance of treatment failure or relapse, despite appropriate treatment, localised disease and anticipated good post-operative lung function. It was felt that the use of these criteria could skew the true treatment effect in either direction. If only those with extensive drug resistance and a high likelihood of treatment failure underwent surgery, then the true treatment effect may favour surgery even more strongly than was actually observed; however, if only those with good lung function underwent surgery, the expected treatment outcomes may be better in this group and the benefits of surgery may be over-estimated. In spite of this uncertainty, the group felt that there may be a role for surgery in the management of some patients with drug resistant disease. It was felt that these patients should be defined by the same characteristics used in the identified evidence. Additionally, it was noted that surgery should not be considered too late in the treatment process. Although surgery should not be undertaken without attempting chemotherapy alone, the possibility of surgery should be considered early in order to prepare the patient, ensuring that, for example, their nutritional status is at an appropriate level.
Trade-off between net health benefits and resource use	Owing to the poor quality and quantity of clinical evidence, and the fact that no health economic evidence was returned from the searches for these questions, the GDG was unable to consider in detail whether there would be any trade-offs between net health benefits and resource use. Surgery is not widely indicated or routinely used to treat TB in the UK; therefore the cost impact of these recommendations is likely to be small.
Quality of evidence	The evidence base suffered from the presence of significant confounding factors and a lack of generalisability to the UK context. A notable source of possible confounding was the variation of the intervention and comparator regimens by more than the presence or absence of surgery. This weakened the strength of the limited evidence available, meaning that it did not exactly match the intervention of interest – an issue subsequently reflected in the appraisal of the quality of the evidence. Other potential confounding factors included the clinical criteria upon which allocation to surgery was frequently based, imbalances in baseline characteristics, and the presence of comorbidities such as renal disease or diabetes that might affect the choice or management of treatment Furthermore, the regimens used in studies of populations with drug susceptible TB did not always use the standard regimen of drugs, as recommended by NICE . This standard regimen consists of 4 drugs: isoniazid and rifampicin for the full treatment period, supplemented by pyrazinamide and ethambutol for the first 2 months of treatment. Deviation of the regimens under examination from this framework limited the applicability of the evidence to UK practice; this was also reflected in the appraisal of the quality of the evidence. Overall, the quality of evidence for all outcomes was defined as 'very low'. The available outcome data came primarily from observational studies or case series, which are not considered to be the 'gold standard' designs for assessing treatment effectiveness. It was noted that small observational studies and case series such as those included can be useful in that they demonstrate a precedence for using surgery; despite this, their specificity to the patients and

context upon and in which they were conducted, as well as their inherent methodological limitations, mean that making recommendations based upon case series could be considered to be over-generalising very individualised data, which the GDG considered to be inappropriate.

In addition to the general methodological limitations associated with these study designs, a significant concern was that the decision to perform surgery in most of these studies was based on a patient's clinical status and suitability to surgery. That is, when a patient needed surgery, they underwent surgery, and when they did not need surgery, they received antituberculosis chemotherapy alone; in this way, the groups were not comparable at baseline and the treatment effects observed cannot be meaningfully compared.

There was also a significant lack of methodological detail in many of the papers, with limited reporting of details relating to baseline comparability of the groups and the duration of follow-up for each group. This means that the quality of the studies is difficult to appraise, and the quality of evidence was downgraded.

There were a number of issues with the interventions used that made the evidence less directly applicable to UK practice: most commonly, the regimens did not use all of or just the 4 standard recommended drugs, and in a number of studies the regimens in the two groups did not differ by the presence or absence of surgery alone.

In addition to the 'indirectness' arising from issues relating to the interventions used, indirectness was also introduced by a number of the papers included in the drug susceptible reviews due to the inclusion of a small proportion of patients with single or combined drug resistance at baseline. These patients can be more difficult to treat and may be confounding the estimates of treatment effect for patients with drug susceptible disease. Additionally, some papers included a small number of patients with comorbidities or coexisting conditions that may affect the choice or management of treatment; these patients further contributed to the indirect nature of some of the evidence.

Additionally, a number of substitute outcomes were extracted by the reviewer, including 'response to treatment'. 'Response to treatment' was considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure, although the exact focus of the outcome definitions used varied widely and often also incorporated changes in the signs and symptoms of disease.

The significant variations in the populations and interventions used across the studies, as well as variations in the definitions of outcome, meant that meta-analysis was not possible.

The GDG also noted the small sample sizes used in a number of studies, which they felt may further reduce the sensitivity to detect differences in the effectiveness of different treatment durations. The small number of events recorded in many of the studies support the suggestion that the included studies were underpowered.

Drug susceptible, spinal tuberculosis:

The GDG noted that, in people with spinal tuberculosis, surgery is generally performed to either remove disease diseased tissue or to correct a deformity. The group felt that in the first case, the removal of diseased tissue, evidence from randomised controlled trials is essential so as to determine the effectiveness of the intervention in achieving a cure and preventing mortality. Conversely, evidence concerning the rate of complications would be more useful to decision-making when the surgery in question is to correct a deformity since this, unlike the presence of disease, is not a life-threatening state, and the GDG felt that the trade-off between benefits and harms associated with performing an invasive operation which has a high level of associated risk may be less justified.

Although the GDG noted the usefulness of the trial evidence identified, the group felt that, overall, the evidence was limited. There was a lack of evidence relating to quality of life, which can be significantly impacted by the decision to perform surgery or not. Additionally, the available outcome data came primarily

from observational studies or case series, which are not considered to be the 'gold standard' designs for assessing treatment effectiveness.

Drug susceptible, central nervous system tuberculosis:

No trial evidence was identified; the review included 4 observational studies.

All evidence relates to the use of shunt surgery in patients with tuberculous meningitis and hydrocephalus. No evidence was found for other forms of central nervous system tuberculosis or for other types of surgery. Additionally, it was felt that to make recommendations on the use of shunt surgery in the management of hydrocephalus would require a review that goes beyond patients with tuberculosis alone, taking into account all causes of hydrocephalus.

Allocation to receive shunt was based on confounding factors: all patients who qualified to receive shunt had hydrocephalus, and therefore by definition had more severe disease than those who did not qualify to undergo surgery.

Drug susceptible, bone and joint tuberculosis:

The available evidence was extremely limited, with just 2 small observational studies included – a retrospective cohort of 30 patients and a case series of 16 patients.

In addition to the methodological limitations generally associated with these study designs, the available data was further limited by a significant amount of heterogeneity in the interventions used, the populations studied and the outcomes reported.

No outcome data was available for mortality, cure or treatment failure.

Drug susceptible, genitourinary tuberculosis:

The available evidence was again limited, with just 2 small observational studies included.

No outcome data was available for mortality or for changes in the signs and symptoms of disease.

Drug susceptible, pulmonary tuberculosis:

A single, retrospective study examining the use of surgery in patients with pulmonary tuberculosis was identified. The specific regimen(s) of antituberculosis drugs used were not reported, but given the time and location of the study (Poland, 1972), the GDG felt that it is unlikely that rifampicin was included. They felt that this severely limited the applicability of the evidence to current UK practice.

The group's confidence in the data was further limited by their uncertainty as to how 'cure' and 'treatment failure' were being defined in the study. Given that these definitions were not reported, the GDG was unable to make a judgement on whether or not the definitions (and therefore the data) were reliable.

For these reasons, as well as the paucity of available data, the GDG did not feel able to make a recommendation on the use of resection in patients with drug susceptible, pulmonary tuberculosis.

Drug susceptible, endobronchial tuberculosis:

The intervention studied (argon plasma coagulation) was felt to be a rare tool with limited relevance to current UK practice. Data was reported only for changes to the signs and symptoms of disease (improvement, deterioration or recurrence of endobronchial lesions), not for any other outcome of interest, limiting the ability of this single study to guide decision-making.

Drug susceptible, chest wall tuberculosis:

The GDG felt that the single case series found was too small to draw any conclusions about the adjunctive use of surgery in patients with active, drug susceptible, chest wall tuberculosis. The sample size was just 7, with only 1

	patient receiving antituberculosis chemotherapy alone. Data was reported only for the incidence of 'good outcomes' (a definition for which was not provided), not for any other outcome of interest, limiting the ability of this single study to guide decision-making. The available outcome data was considered to be very low in quality. **Drug resistant tuberculosis:** The study populations were primarily concerned with pulmonary tuberculosis; very few patients with extrapulmonary tuberculosis were included in the evidence base. The included studies were predominantly conducted in countries that more readily use surgery in the management of tuberculosis. It was felt that this may limit the applicability of the evidence to the UK context. No evidence was found for key subgroups of interest, including children and young people and people with HIV. Data for some of outcomes of interest, in particular that relating to rates of operative and post-operative complications, was limited. In order to be considered for surgery, patients in many studies had to fulfil a number of clinical criteria, including extensive drug resistance, a high chance of treatment failure or relapse, despite appropriate treatment, localised disease and anticipated good post-operative lung function. These criteria reflect potentially confounding factors, although it is unclear in which direction the treatment effect may have been skewed overall. This uncertainty is further compounded by the lack of information relating to the comparability of the surgical and non-surgical groups at baseline.
Other considerations	None.

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4.8.71 Recommendations

72. If surgery is indicated, the surgeon should fully explain what is involved to the person, either with or after consulting a TB specialist. Discuss the possible benefits and risks with the person and their family members or carers, as appropriate, so that they can make an informed decision. [new 2015]

Central nervous system TB

73. Consider surgery as a therapeutic intervention in people with TB of the central nervous system only if there is evidence of raised intracranial pressure. [new 2015]

Spinal TB

74. Do not routinely perform surgery in people with spinal TB to eradicate the disease. [new 2015]

75. Consider surgery in people with spinal TB if there is spinal instability or evidence of spinal cord compression. [new 2015]

Drug resistant TB

76. Consider surgery as a therapeutic intervention in people with potentially resectable multidrug-resistant disease if:

- optimal medical therapy under direct observation has not worked, or

- medical therapy is likely to fail because of extensively drug-resistant TB. **[new 2015]**

Update 2015

4.9 Treatment of active tuberculosis in people with comorbidities or co-existing conditions

This section reviews the key issues associated with choosing a treatment regimen for people with tuberculosis and a key comorbidity or co-existing condition; specifically, the GDG were to consider possible ways in which the standard recommended regimen can be adapted to accommodate HIV coinfection, the presence of coexisting liver disease, renal disease, diabetes, impaired vision or eye disease, substance use, pregnancy or breast-feeding. This information will be summarised according to the comorbidity or co-existing condition, to create an accessible outline of the possible issues that might arise in the comanagement of these conditions.

These comorbidities and co-existing conditions were selected by the GDG due to the severity of the consequences of mismanagement, the prevalence of the comorbidity or co-existing condition amongst people with TB, or the concerns raised by patients, carers and healthcare professionals.

4.9.1 People coinfected with tuberculosis and HIV

4.9.1.1 Clinical introduction

The most recent year for which TB-HIV co-infection data are available for England, Wales and Northern Ireland is 2011, and in that year 3.6% of people with tuberculosis were co-infected with HIV. Further to this, a number of drugs used in the treatment of these diseases are known to be linked to the same metabolic pathways in the liver, impacting the availability of the drugs in the body, as well as being associated with similar toxicity profiles. This evidence review focused on how the standard combination of antituberculosis drugs can be adapted to accommodate coinfection with, and comanagement of, HIV.

Update 2015

4.9.1.2 Review question

In people co-infected with drug susceptible, active TB and HIV receiving drug treatment for both infections, what are the key pharmacological considerations that should be taken into account when selecting a treatment regimen for treating active or latent TB?

4.9.1.3 Evidence review

The evidence review for this section includes:

- Systematic reviews of randomised and quasi-randomised controlled trials, as well as existing meta-analyses of randomised and quasi-randomised controlled trials; if insufficient evidence was found, non-randomised controlled trials and prospective cohort studies were also considered. These reviews will be summarised and presented, as for the other clinical reviews in this guidance, in line with the process and methods described in The Guidelines Manual.
- Reviews of the British National Formulary (BNF) and the Summaries of Product Characteristics (SPCs) for:
  - information relating to the use of the 4 standard recommended drugs – rifampicin, isoniazid, pyrazinamide and ethambutol – in people with the comorbidities and co-existing conditions of interest;
  - pharmacological information relating to drug interactions and overlapping toxicity profiles in people receiving treatment for both HIV and tuberculosis.

4.9.1.3.1 Systematic review

Papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all relevant papers. Randomised, quasi-randomised and non-randomised controlled trials, as well as prospective cohort studies, comparing different treatment regimens for TB in patients coinfected with active, drug susceptible TB and HIV were considered for inclusion. (See Appendix C for the full review protocol).

Trials were excluded if:

- the population included people with latent TB or drug resistant TB;
- trials had a sample of 30 or less and could not be included in a meta-analysis;
- papers considered the use of drugs not licensed in the UK; or
- study designs were retrospective observational studies, case studies or narrative reviews.

From a database of 3838 abstracts, 218 full-text articles were ordered, which covered all 7 comorbidities or co-existing conditions of interest, and 5 papers relating to the treatment of TB in patients coinfected with HIV were included (See Appendix D for details of the included studies).

4.9.1.3.2 Review of information in the BNF and SPCs

This review sought to summarise key pharmacological considerations raised within the BNF and SPCs of antiretroviral and first-line antituberculosis drugs with regards to drug interactions and overlapping toxicity profiles in people receiving treatment for both HIV and tuberculosis.

The first table is a summary of potential issues that can arise in the co-administration of the relevant drugs. The second table provides information on why these issues occur, as well as more detail on the action required.

Table 18: Treatment of people with HIV and active or latent tuberculosis: summary of actions for co-administration of HIV drugs and first-line antituberculosis drugs

HIV drug	Rifampicin	Rifabutin	Isoniazid	Pyrazinamide	Ethambutol	Streptomycin
Entry inhibitors						
Enfuvirtide						
Integrase inhibitors						
Dolutegravir						
Elvitegravir						
Raltegravir						
Non-nucleoside reverse transcriptase inhibitors						
Efavirenz						
Etravirine						
Nevirapine						
Rilpivirine						
Nucleoside reverse transcriptase inhibitors						
Abacavir						
Didanosine						
Emtricitabine						
Lamivudine						
Stavudine						
Tenofovir						
Zidovudine						

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HIV drug	Rifampicin	Rifabutin	Isoniazid	Pyrazinamide	Ethambutol	Streptomycin
Protease inhibitors						
Atazanavir						
Darunavir						
Fosamprenavi						
Indinavir						
Lopinavir with ritonavir						
Ritonavir						
Boosted saquinavir						
Unboosted saquinavir						
Tipranavir						
Other						
Maraviroc						
KEY:						
No significant issues	Caution advised		Dose adjustment and monitoring advised		Co-administration not recommended	

Table 19: Pharmacological considerations for people with HIV who are being treated for active or latent tuberculosis – information from the British National Formulary and the Summary of Product Characteristics: drugs used for the treatment of HIV

Drug	Pharmacological issues	Recommended action
Entry inhibitors		
Enfuvirtide	No significant issues noted	
Integrase inhibitors		
Dolutegravir	UGT 1A1 metabolism: Co-administration with UGT 1A1 inducers reduces plasma levels of dolutegravir	Rifampicin: Dose adjustment: double dose of dolutegravir if co-administered with rifampicin in the absence of integrase class resistance Co-administration not recommended in the presence of integrase class resistance Rifabutin: No dose adjustment is necessary
Elvitegravir	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease elvitegravir plasma concentrations and increase concentrations of CYP3A inducers	Rifampicin: Co-administration not recommended Rifabutin: Co-administration not recommended If the combination is needed, reduce the dose of rifabutin and monitor for rifabutin-associated adverse reactions, including neutropenia and uveitis, and the emergence of rifamycin resistance or treatment failure
Raltegravir potassium	UGT 1A1 metabolism: Co-administration with UGT 1A1 inducers reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown	Co-administration with UGT 1A1 inducers should be done with caution Rifampicin: If co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults
Nucleoside reverse transcriptase inhibitors		
Abacavir sulphate	UGT 1A1 metabolism:	Rifampicin:

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Drug	Pharmacological issues	Recommended action
	Co-administration with UGT 1A1 inducers reduces plasma levels of abacavir	Co-administration of abacavir with UGT 1A1 inducers should be done with caution, though standard doses can be used Rifabutin: Co-administration of abacavir with UGT 1A1 inducers should be done with caution Clearance of abacavir is predicted to be to a lesser extent than for rifampicin, though standard doses can be used
Didanosine	Risk of peripheral neuropathy	Isoniazid: Alternatives to didanosine should be given to patients taking isoniazid
Emtricitabine	No significant issues noted	
Lamivudine	No significant issues noted	
Stavudine	Risk of peripheral neuropathy	Isoniazid: Co-administration not recommended
Tenofovir disoproxil fumarate	Risk of renal failure	Streptomycin: Co-administration not recommended
Zidovudine	No significant issues noted	No significant issues noted
Non-nucleoside reverse transcriptase inhibitors		
Efavirenz	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease efavirenz or CYP3A inducer plasma concentrations	Rifampicin: Dose adjustment: increase dose of efavirenz; no dose adjustment is necessary for rifampicin Rifampicin reduces efavirenz concentrations; therapeutic failure has been reported in some patients Concurrent use should be closely monitored for virological efficacy and adverse effects Rifabutin: Dose adjustment: dose of rifabutin should be increased Rifabutin does not affect efavirenz concentrations, but efavirenz decreases rifabutin exposure: cases of subtherapeutic rifabutin concentrations and tuberculosis treatment failure have resulted
Etravirine	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease etravirine plasma concentrations	Rifampicin: Co-administration not recommended Rifabutin: No initial dose adjustment of either drug is needed, but close monitoring for response to both treatments is recommended
	Required cotreatments: Should be used in combination with a boosted protease inhibitor	Rifampicin: Rifampicin is contraindicated in combination with boosted PIs: co-administration with etravirine therefore also not recommended
Nevirapine anhydrate and hemihydrate	CYP3A metabolism: Co-administration with CYP3A inducers may	Rifampicin: Co-administration not recommended

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Drug	Pharmacological issues	Recommended action
	significantly decrease nevirapine plasma concentrations	Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen may consider co-administration of rifabutin instead; if concurrent use is unavoidable, give standard doses and monitor nevirapine concentrations Rifabutin: Rifabutin and nevirapine can be co-administered without dose adjustments; however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity – caution should be used in concomitant administration
Rilpivirine hydrochloride	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease in rilpivirine plasma concentrations due to CYP3A enzyme induction or gastric pH increase	Rifampicin: Co-administration not recommended Rifabutin: Co-administration should be avoided However, if use is essential, rilpivirine efficacy should be monitored and the dose of rilpivirine amended as appropriate
Protease inhibitors		
Atazanavir sulphate	CYP3A metabolism: Co-administration with rifampicin, a CYP3A inducer, may significantly decrease atazanavir plasma concentrations	Rifampicin: Co-administration not recommended
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration with atazanavir can lead to increases in rifabutin plasma concentrations	Rifabutin: Dose adjustment: reduce dose of rifabutin Increased monitoring for rifabutin-associated adverse reactions, including arthralgia, increased liver enzymes, uveitis, and leucopenia, and the emergence of rifamycin resistance or treatment failure is warranted No dose adjustment is needed for atazanavir
Darunavir ethanolate	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease darunavir plasma concentrations	Rifampicin: Co-administration not recommended
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration with darunavir can lead to increases in rifabutin plasma concentrations	Rifabutin: Dose adjustment: reduce dose of rifabutin Increased monitoring for rifabutin-associated adverse reactions, including including arthralgia, increased liver enzymes, uveitis, and leucopenia, and the emergence of rifamycin resistance or treatment failure is warranted No dose adjustment is needed for darunavir

Drug	Pharmacological issues	Recommended action
Fosamprenavi calcium	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease fosamprenavi plasma concentrations	Rifampicin: Co-administration not recommended
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration with fosamprenavi can lead to increases in rifabutin plasma concentrations	Rifabutin: Dose adjustment: reduce dose of rifabutin Increased monitoring for rifabutin-associated adverse reactions, including neutropenia and uveitis, and the emergence of rifamycin resistance or treatment failure is warranted
Indinavir sulphate	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease indinavir plasma concentrations	Rifampicin: Co-administration not recommended Rifabutin: Co-administration not recommended
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration with indinavir can lead to increases in rifabutin plasma concentrations	Rifabutin: Co-administration not recommended If use is essential, reduce dose of rifabutin and monitor for rifabutin-associated adverse reactions, including neutropenia and uveitis, and the emergence of rifamycin resistance or treatment failure
Lopinavir with ritonavir	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease lopinavir and ritonavir plasma concentrations	Rifampicin: Co-administration not recommended
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration can lead to increases in rifabutin plasma concentrations	Rifabutin: Reduce dose of rifabutin and monitor for rifabutin-associated adverse reactions, including neutropenia and uveitis, and the emergence of rifamycin resistance or treatment failure
Ritonavir	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease ritonavir plasma concentrations	Rifampicin: Co-administration not recommended If use is essential, rifampicin can be given with ritonavir 600 mg twice daily, but it is poorly tolerated; monitor for both ritonavir efficacy and toxicity
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration with ritonavir can lead to increases in rifabutin plasma concentrations	Rifabutin: Co-administration not recommended If use is essential, reduce dose of rifabutin and monitor for rifabutin-associated adverse reactions, including neutropenia and uveitis, and the emergence of rifamycin resistance or treatment failure
Saquinavir mesilate	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease	Rifampicin: Co-administration not recommended

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Drug	Pharmacological issues	Recommended action
	saquinavir plasma concentrations	
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration with saquinavir can lead to increases in rifabutin plasma concentrations	Rifabutin: Unboosted saquinavir should not be used with rifabutin Saquinavir boosted with ritonavir: reduce dose of rifabutin; increased monitoring for rifabutin-associated adverse reactions, including neutropenia and liver toxicity, and the emergence of rifamycin resistance or treatment failure is warranted No dose adjustment is needed for saquinavir, though monitoring of plasma concentrations is recommended
Tipranavir	CYP3A metabolism: Co-administration with CYP3A inducers may significantly decrease tipranavir plasma concentrations	Rifampicin: Co-administration not recommended
	Since rifabutin is also a substrate of the CYP3A enzyme, co-administration with tipranavir can lead to increases in rifabutin plasma concentrations	Rifabutin: Co-administration not recommended If use is essential, reduce dose of rifabutin and monitor for rifabutin-associated adverse reactions, including neutropenia and uveitis, and the emergence of rifamycin resistance or treatment failure No dose adjustment is needed for tipranavir
Other		
Maraviroc	CYP3A metabolism: Co-administration with rifampicin may significantly decrease maraviroc plasma concentrations	Rifampicin: Increase dose of maraviroc
	CYP3A metabolism: When combining rifabutin with protease inhibitors that are potent inhibitors of CYP3A4 a net inhibitory effect on maraviroc is expected	Rifabutin + protease inhibitors: Decrease dose of maraviroc

Update 2015

4.9.1.42 Evidence statements

Low quality of evidence from 1 randomised controlled trial of 50 patients coinfected with TB and HIV comparing a rifabutin-containing regimen (2HRbZE/4HRb; for an explanation of the abbreviation system for treatment strategies, see section 13.2) with the standard regimen (2HRZE/4HR) was inconclusive about which combination of drugs was the most effective in terms of reducing mortality, or improving radiographic status or the rate of sputum conversion.

Very low quality of evidence from 1 randomised controlled trial of 58 patients coinfected with TB and HIV comparing a ciprofloxacin-containing regimen (4HRC/2HR) with the standard regimen (2HRZE/2HRZ/2HR) was inconclusive about which combination of drugs was the most effective in terms of reducing the incidence of relapse or improving the time to sputum conversion.

Very low quality of evidence from 1 prospective cohort study in patients coinfected with TB and HIV comparing non-rifampicin-containing regimens (at least H and Z) with rifampicin-containing regimens (at least HRZ) was inconclusive about which combination of drugs was the most effective in terms of reducing mortality.

Very low quality of evidence from 1 randomised controlled trial and 1 prospective cohort study in patients coinfected with TB and HIV comparing a regimen with an ethambutol-containing continuation phase (2HRZE/6HE) with the standard regimen (2HRZE/4HR or 2HRZE/6HR) was inconclusive about which combination of drugs was the most effective in terms of reducing mortality and treatment failure, although the regimen with the ethambutol-containing continuation phase was associated with a higher rate of relapse and poorer adherence.

4.9.1.17 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. Relapse, changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of TB.
Trade-off between benefits and harms	The group also noted that evidence showed the use of regimens with ethambutol- rather than rifampicin-containing continuation phases to be associated with worse outcomes, such as relapse and poor rates of treatment completion. Additionally, the GDG felt that this had been the case in their own clinical experience. However, they did not feel that the evidence was strong enough to make a recommendation against the use of ethambutol- rather than rifampicin-containing continuation phases, particularly given their potential usefulness in patients receiving antiretroviral regimens known to interact with rifampicin. The pharmacological considerations identified in the BNF and the SPCs largely concern interactions between a number of antiretroviral drugs and the rifamycins. Most of these interactions occur through the induction or inhibition of metabolic enzymes in the liver, and the most important family of enzymes is CYP450. The CYP3A4 isoform metabolises many drugs, including protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Rifampicin is a powerful inducer of CYP3A and, to a lesser extent, CYP2C19 and CYPD6; rifabutin is also a CYP3A inducer, though less strongly so and may therefore be used as an alternative to overcome some of these difficulties. These interactions are linked to decreases in the availability of the HIV drugs, and are therefore associated with increased risks of virological failure and the development of resistance. When doses of the HIV drug have been increased in an attempt to overcome this, increases in liver reactions were observed. Unlike rifampicin, rifabutin is also a substrate of CYP3A4; any CYP3A4 inhibitors, such as the protease inhibitors, will therefore increase levels of rifabutin in the body and may cause toxicity. Both rifampicin and rifabutin are also UGT (UDP glucuronosyltransferase) 1A1 inducers. Therefore, interactions may also arise when they are co-

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	administered with other drugs involved with the UGT 1A1 enzymes, including a number of integrase inhibitors and nucleoside reverse transcriptase inhibitors. Therapeutic drug monitoring should be performed when drug regimens are complex. Levels of HIV and antituberculosis drugs should be measured when there is clinical concern regarding absorption or response to those drugs. Further to these drug interactions, the toxicity profiles of antiretrovirals and antituberculosis drugs overlap and this make it difficult to determine the causative drug. Rash, fever and hepatitis are common side effects of antituberculosis drugs, especially rifampicin, isoniazid and pyrazinamide; non-nucleoside reverse transcriptase inhibitors cause similar adverse reactions. Isoniazid and a number of nucleoside reverse transcriptase inhibitors are associated with an increased risk of peripheral neuropathy; all patients receiving isoniazid should take pyridoxine to prevent this. Additionally, stavudine and didanosine should not be given in the treatment of people coinfected with tuberculosis and HIV due to the significance of the risk of peripheral neuropathy when taken with isoniazid. Non-nucleoside reverse transcriptase inhibitors are mostly free of clinically significant interactions with rifampicin and rifabutin, and no pharmacological issues were found relating to the use of antiretroviral chemotherapy and ethambutol or pyrazinamide. The GDG felt that the complexity of drug-drug interactions, and the overlaps that exist in toxicity profiles, requires expertise in the concomitant use of antiretroviral and antituberculosis chemotherapy as the consequences of mismanagement can be severe. Specialist input should happen as early as possible, though initiation of antituberculosis chemotherapy (using the standard recommended regimens) should not be delayed. The group also felt that it is important that clinicians clearly communicate such risks to each patient, discussing the potential benefits and harms – including possible drug interactions and overlapping toxicity profiles – of different approaches to co-treatment, and ensuring the patient's input into decision-making. An additional principle emphasised by the GDG relates to continuity of treatment: in patients on a stable antiretroviral regimen at the time that tuberculosis is diagnosed or at the time antituberculosis chemotherapy is to be initiated, it is generally the choice of antituberculosis drugs that should be tailored when attempting to reduce issues relating to toxicity and interactions. Disruptions to a stable antiretroviral regimen should be avoided.
Trade-off between net health benefits and resource use	Fororthe reasons detailed in the "Other Considerations" section it is unlikely these recommendations will incur additional trade-offs between net health benefit and resource use, as they reflect current practice. In addition, no applicable health economic evidence was identified in the literature search for this question.
Quality of evidence	Overall, the quality of evidence for all outcomes was defined as 'low' or 'very low'. No evidence was found for the key subgroup of interest (that is, children and young people). Additionally, the interaction studies informing the British National Formulary and the Summaries of Product Characteristics for antiretroviral and first-line antituberculosis drugs were performed only in adults. The evidence base suffered from the presence of significant confounding factors, such as the variation of the intervention and comparator regimens by more than the combination of antituberculosis drugs used: some regimens also varied by duration and/or dosing frequency, and the additional care received by each group, such as the supervision of treatment, was not always comparable. This weakened the strength of the limited evidence available, and was reflected in the appraisal of the quality of the evidence. Furthermore, the combination of drugs used in the comparator regimens did

	not always use all 4 of the standard regimen of drugs. Deviation of the comparator regimens from the standard recommended regimen limited the applicability of the evidence to UK practice; this was also reflected in the appraisal of the quality of the evidence. There was also a significant lack of methodological detail in a number of the papers, with limited reporting of details relating to baseline comparability of the groups, the duration of follow-up for each group, the definitions of outcome and the tools with which they are assessed, the exact interventions used and the supplementary care. This means that the quality of the studies is difficult to appraise, and the quality of evidence was downgraded. Where methodological details were reported, there were a number of issues that contributed to the low quality of the evidence. Firstly, the participants, caregivers and investigators were not always blinded to the treatments received or relevant prognostic factors. Groups were not always followed up for the same length of time, were not comparable at baseline and, in the case of the included observational studies, attempts were not made to balance them in the analyses. Additionally, a number of substitute outcomes, including 'response to treatment', were extracted by the reviewer because they were considered to be a potentially useful substitute outcome for cure, treatment success and/or treatment failure. The significant variations in the populations and interventions used across the studies, as well as variations in the definitions of outcome, meant that meta-analysis was not possible. The GDG also noted the small sample sizes used in a number of studies, which they felt may further reduce the sensitivity to detect differences in the effectiveness of different regimens. The small number of events recorded in many of the studies support the suggestion that the included studies were underpowered. The GDG felt it important that clinicians involved in such decisions refer to the most up-to-date information available. New pharmacological data relating to the concomitant use of antiretroviral and antituberculosis chemotherapy is constantly emerging, and the BNF and SPC summaries presented here are up-to-date only as far as the date at which this guidance was published.
Other considerations	The GDG felt that the systematic review did not provide sufficient evidence to deviate from current recommendations (that is, the standard recommended regimen) for the treatment of tuberculosis in patients coinfected with HIV, including those patients not receiving antiretroviral therapy.

(a) <Insert Note here>

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4.9.1.6 Recommendations

77. If the person has a comorbidity or coexisting condition such as:

- HIV, or
- severe liver disease, for example, Child-Pugh level B or C, or
- stage 4 or 5 chronic kidney disease (a glomerular filtration rate of <30 ml/minute/1.73m^2), or
- diabetes, or
- eye disease or impaired vision, or
- pregnancy or breastfeeding, or
- a history of alcohol or substance misuse

work with a specialist multidisciplinary team with experience of managing TB and the comorbidity or coexisting condition. **[new 2015]**

78. For people with HIV and active TB without central nervous system involvement, do not routinely extend treatment beyond 6 months. [new 2015]

79. For people with HIV and active TB with central nervous system involvement, do not routinely extend treatment beyond 12 months. [new 2015]

80. Take into account drug-to-drug interactions when co-prescribing antiretroviral and anti-TB drugs. [new 2015]

4.9.1.7 Research recommendations

7. How should the standard recommended regimen for active TB be adapted to accommodate comorbidities or coexisting conditions?

Why this is important

NICE conducted an evidence review into the most effective regimens for active TB in people with comorbidities or coexisting conditions (including HIV, liver disease, renal disease, diabetes, substance use, including methadone use, pregnancy and breastfeeding and impaired vision or eye disease), but did not identify any evidence. People in these groups are at increased risk of drug–drug, and do not respond to anti-TB therapy in the same was as those without a comorbidity or coexisting condition. They may therefore need an adapted regimen to improve the likelihood of treatment success and reduce the risk of adverse events. Randomised controlled trials are needed to compare the standard recommended regimen with alternatives for active TB in these people. Alternatively, given the relatively small numbers of people in these groups, prospective observational cohort studies could be conducted to assess treatment success and adverse events for different regiments.

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4.9.21 People with tuberculosis and liver disease

4.9.2.12 Clinical introduction

This population is of particular interest because some antituberculosis drugs are metabolised in the liver. Achieving adequate treatment of tuberculosis is therefore more difficult and may be associated with a higher incidence of adverse events. This evidence review focused on how the standard combination of antituberculosis drugs can be adapted to accommodate coexisting liver disease.

4.9.2.28 Review question

How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB?

4.9.2.32 Evidence review

As for the review in people coinfected with HIV, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all relevant papers. Randomised, quasi-randomised and non-randomised controlled trials, as well as prospective cohort studies, comparing different treatment regimens for tuberculosis in patients with active, drug susceptible TB and liver disease were considered for inclusion. (See Appendix C for the full review protocol). Exclusion criteria were as above for the review in people coinfected with HIV.

From a database of 3838 abstracts, 218 full-text articles were ordered, which covered all 7 comorbidities or co-existing conditions of interest, and 2 papers relating to the treatment of TB in patients with coexisting liver disease were included. (See Appendix D for details of the included studies.

4.9.2.46 Evidence statements

Very low quality of evidence from 1 randomised controlled trial and 1 prospective cohort study in patients with TB and coexisting liver disease comparing a regimen with an fluoroquinolone-containing regimen (2HZEO/10HEO or HRbAOL) with the standard regimen (2HRE/7HR or HRZS/E) was inconclusive about which combination of drugs was the most effective in terms of reducing mortality, although in the observational study the standard regimen was associated with a greater incidence of hepatotoxicity.

4.9.2.53 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. Relapse, changes in the signs and symptoms of tuberculosis, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of tuberculosis.
Trade-off between benefits and harms	The treatment considerations identified in the BNF and the SPCs largely relate to the increased risk of hepatotoxicity associated with all 4 of the standard recommended drugs. The GDG support the assertion that caution is therefore required when using them in patients with liver disease.

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	In line with the advice provided within the BNF and SPCs, the GDG felt that hepatic function should be checked before treatment, and those with pre-existing liver disease should be frequently monitored, particularly in the initial phase of treatment. They also noted, however, that the impact of antituberculosis drugs on aspartate aminotransferase and alanine aminotransferase levels can complicate the monitoring of liver disease or toxicity; slight fluctuations in these biochemical markers of liver function are to be expected, but the 'background noise' produced by the antituberculosis chemotherapy can cloud interpretation. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or otherwise deteriorates during treatment without explanation. If the symptoms of hepatitis appear or if signs suggestive of hepatic damage are detected, treatment should be discontinued promptly. Little evidence was identified in the systematic review to demonstrate a difference between the different regimens (between fluoroquinolone-containing regimens and the standard combination of drugs) in terms of the incidence of hepatotoxicity. Furthermore, no conclusions could be made with regards to the most effective treatment in terms of achieving cure; the group felt that the ideal regimen would minimise the risk of hepatotoxicity without compromising the treatment of the disease. The group felt that further trials investigating this would be useful to future decision-making. Although it was the opinion of the GDG that current practice in patients at increased risk of hepatotoxicity is to use a fluoroquinolone in place of rifampicin, they did not feel there was sufficient evidence to recommend the use of a fluoroquinolone-containing regimen over the standard regimen in patients with liver disease. The GDG felt that the paucity of evidence, as well as the severity of the consequences should treatment be mismanaged, make specialist input essential in the treatment of tuberculosis in patients with liver disease. Child-Pugh B should be considered the threshold for specialist input as this represents the level at which prognosis becomes significantly affected (that is, survival time is considerably shortened); however, specialist input before this stage would be preferable.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	The evidence identified was very limited, both in its scope and in its quality. Both studies compared fluoroquinolone-containing regimens with the standard combination of drugs; no other combinations were examined. No evidence was found for the key subgroup of interest (that is, children and young people). Additionally, the interaction studies informing the BNF and the SPCs for the first-line antituberculosis drugs were performed only in adults. Overall, the quality of evidence for all outcomes was defined as 'very low'. The evidence base was limited and, again, suffered from the presence of confounding factors, such as the variation of the intervention and comparator regimens by more than the combination of antituberculosis drugs used. This was reflected in the appraisal of the quality of the evidence. Furthermore, the combination of drugs used in the comparator regimens did not use all 4 of the standard regimen of drugs. Deviation of the comparator regimens from the standard recommended regimen limited the applicability of the evidence to UK practice; this was also reflected in the appraisal of the quality of the evidence. There was also a significant lack of methodological detail in the included papers, with limited reporting of details relating to the duration of follow-up for each group, the comparability of the groups at baseline and the supplementary care received by each group. This means that the quality of the studies is difficult to appraise in some areas, and the quality of evidence was downgraded.

	There were a number of issues with the interventions used that made the evidence less directly applicable to UK practice. In the RCT, the fluoroquinolone-containing regimen did not reflect that which would be used in current practice: as stated above, the fluoroquinolone would replace rifampicin, due to concerns over the high risk of hepatotoxicity, not pyrazinamide. In the observational study, the dosing of the fluoroquinolones was lower than would be used in the UK, and the use of rifabutin over rifampicin would not generally be considered in this population. Furthermore, the interventions prescribed to each treatment group varied by more than the combination of antituberculosis drugs used. In the RCT, regimens also varied by total duration of treatment; additionally, it is unclear if the doses used and the dosing frequencies were comparable in the 2 regimens. In the observational study, the 2 regimens used different dosing schedules, and it is unclear if the total duration of treatment was comparable in the 2 groups. This means it is not possible to conclude that any differences in the effects observed in each group arose due to the different combinations of drugs alone. The 'directness' of the evidence was further impaired by the population characteristics of those included in the observational study: participants were non-symptomatic, and therefore cannot truly be said to have liver disease. The GDG also noted the small sample sizes used in a number of studies, which they felt may further reduce the sensitivity to detect differences in the effectiveness of different regimens. The small number of events recorded in many of the studies support the suggestion that the included studies were underpowered.
Other considerations	None.

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4.9.2.6 Recommendations

See section 4.9.1.6

4.9.2.7 Research recommendations

See section 4.9.1.7

4.9.3 People with tuberculosis and renal disease

4.9.3.1 Clinical Introduction

Patients with renal disease are both at increased risk of developing tuberculosis and for that tuberculosis to cause significant morbidity and pathology. This is because the immune response of many renal patients is impaired – either as a result of their renal disease or as a result of immunosuppressive drugs being used. Antituberculosis drugs are therefore crucial in curing patients. The effects of renal disease and/or its treatment may interact with the effects or treatment of the tuberculosis, requiring alterations be made to the management of the patient. This evidence review focused on how the standard combination of antituberculosis drugs can be adapted to accommodate coexisting renal disease.

4.9.3.2 Review question

How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB?

4.9.3.3 Evidence review

As for the review in people coinfected with HIV, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all relevant papers. Randomised, quasi-randomised and non-randomised controlled trials, as well as prospective cohort studies, comparing different treatment regimens for TB in patients with active, drug susceptible TB and renal disease were considered for inclusion. (See Appendix C for the full review protocol). Exclusion criteria were as above for the review in people coinfected with HIV.

From a database of 3838 abstracts, 218 full-text articles were ordered, which covered all 7 comorbidities or co-existing conditions of interest, but no papers relating to the treatment of TB in patients with coexisting renal disease met the inclusion and exclusion criteria.

4.9.3.4 Evidence statements

No evidence was identified.

4.9.3.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. Relapse, changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of TB.
Trade-off between benefits and harms	No evidence comparing the effectiveness of different antituberculosis regimens in patients with renal disease was identified. However, the group noted that some drugs (notably ethambutol) are excreted by the kidneys, so dosages have to be adjusted, and others (notably the aminoglycosides) are toxic to the kidneys, so have to be avoided. The antituberculosis drugs may also be cleared from the body through dialysis. Achieving adequate treatment of tuberculosis is therefore more difficult and,

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	in turn, renal disease may be associated with poorer treatment outcomes due to compromised control of bacillary replication, as well as potential promotion of the development of drug resistance. The lack of evidence coupled with the GDG's awareness of these potential complications meant that they felt that patients with both tuberculosis and renal disease should be managed in conjunction with a specialist multidisciplinary team with experience of managing TB and renal disease.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	No evidence comparing the effectiveness of different antituberculosis regimens in patients with renal disease was identified. The interaction studies informing the BNF and the SPCs for the first-line antituberculosis drugs were performed only in adults.
Other considerations	The lack of evidence meant that the GDG did not feel able to recommend the use of a regimen other than the standard regimen in patients with renal disease. Renal disease or insufficiency complicates the management of tuberculosis because some antituberculosis drugs are cleared by the kidneys. Clearance may also be increased in patients receiving dialysis. For this reason, renal function tests and monitoring of serum uric acid should be performed before treatment and at regular intervals during treatment. Rifampicin, isoniazid and pyrazinamide may generally be given in normal doses because they are either eliminated in the bile or broken down to metabolites that are not excreted by the kidney. By contrast, care is required in the use of ethambutol and streptomycin because these are excreted via the kidney. The use of ethambutol is associated with optic neuritis and reduced doses may be required, according to the level of renal insufficiency. Streptomycin and other aminoglycosides are ototoxic, and should be avoided if possible in patients with renal impairment because they have a high risk of nephrotoxicity. The GDG felt that the lack of evidence, as well as the severity of the consequences should treatment be mismanaged, make specialist input essential in the treatment of tuberculosis in patients with renal disease.

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4.9.3.6 Recommendations

See section 4.9.1.6

4.9.3.7 Research recommendations

See section 4.9.1.7

4.9.4 People with tuberculosis and diabetes

4.9.4.1 Clinical introduction

As for renal disease, patients with diabetes are both at increased risk of developing tuberculosis and for that tuberculosis to cause significant morbidity and pathology. This is because the immune response of many patients with diabetes is impaired. Treatment of tuberculosis can be more difficult in patients with diabetes, and those with diabetes can be at risk for poorer treatment outcomes compared to those who do not have diabetes.

This evidence review focused on how the standard combination of antituberculosis can be adapted to accommodate coexisting diabetes.

4.9.4.2 Review question

How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB?

4.9.4.3 Evidence review

As for the review in people coinfected with HIV, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all relevant papers. Randomised, quasi-randomised and non-randomised controlled trials, as well as prospective cohort studies, comparing different treatment regimens for TB in patients with active, drug susceptible tuberculosis and diabetes were considered for inclusion. (See Appendix C for the full review protocol). Exclusion criteria were as above for the review in people coinfected with HIV.

From a database of 3838 abstracts, 218 full-text articles were ordered, which covered all 7 comorbidities or co-existing conditions of interest, but no papers relating to the treatment of TB in patients with coexisting diabetes met the inclusion and exclusion criteria.

4.9.4.4 Evidence statements

No evidence was identified.

4.9.4.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. Relapse, changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of tuberculosis.
Trade-off between benefits and harms	No evidence comparing the effectiveness of different antituberculosis regimens in patients with diabetes was identified. However, the group noted that, as for renal disease, treatment of tuberculosis can be more difficult in patients with diabetes – for example, due to diabetic complications, such as renal failure, or because of the similar adverse effect profiles of antituberculosis drugs and diabetes, such as peripheral neuropathy, or because of interactions between the treatments used for the 2

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	conditions. For these reasons, those with diabetes can be at risk for poorer treatment outcomes – including treatmenmt failure, trelapse or the development of drug resistance – compared to those who do not have diabetes. The lack of evidence coupled with the GDG's awareness of these potential complications meant that they felt that patients with both tuberculosis and diabetes should be managed in conjunction with a specialist multidisciplinary team with experience of managing TB and diabetes.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	No evidence comparing the effectiveness of different antituberculosis regimens in patients with diabetes was identified. The interaction studies informing the BNF and the SPCs for the first-line antituberculosis drugs were performed only in adults.
Other considerations	Treatment of tuberculosis is more difficult in patients with diabetes, and can be associated with poorer treatment outcomes compared to those who do not have tuberculosis. One possible explanation for this may be the compromised immunity of patients with diabetes. Furthermore, infections are known to worsen diabetic control. The BNF and SPCs for isoniazid also highlight the increased risk of hyperglycaemia associated with use of the drug, as well as increased difficulties in controlling the diabetes. Co-existing diabetes and its treatment is also a risk factor for peripheral neuropathy due to overlapping toxicity profiles with isoniazid, and those with diabetes should therefore receive prophylactic pyridoxine when taking isoniazid. The GDG felt that the lack of evidence, as well as the severity of the potential consequences of mismanagement, make specialist input essential in the treatment of tuberculosis in patients with diabetes.

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4.9.4.6 Recommendations

See section 4.9.1.6

4.9.4.7 Research recommendations

See section 4.9.1.7

4.9.5 People with tuberculosis who are substance misusers

4.9.5.1 Clinical introduction

A significant proportion of people with tuberculosis are also substance misusers; in 2012 in the UK, Public Health England report that 2.8% of people with tuberculosis had a history of problem drug use and 3.2% were known to misuse or abuse alcohol. Substance misuse is known to be associated with an impaired immune response, and so is associated with an increased risk of developing tuberculosis and for that tuberculosis to cause significant morbidity and pathology. Additionally, the toxicity profiles of these substances are known to overlap with those for the first-line antituberculosis drugs. This evidence review focused on how the standard combination of antituberculosis can be adapted for people who are substance misusers.

4.9.5.2 Review question

How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB?

4.9.5.3 Evidence review

As for the review in people coinfected with HIV, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all relevant papers. Randomised, quasi-randomised and non-randomised controlled trials, as well as prospective cohort studies, comparing different treatment regimens for TB in patients with active, drug susceptible TB and who are substance misusers were considered for inclusion. (See Appendix C for the full review protocol). Exclusion criteria were as above for the review in people coinfected with HIV.

From a database of 3838 abstracts, 218 full-text articles were ordered, which covered all 7 comorbidities or co-existing conditions of interest, but no papers relating to the treatment of TB in people who are substance misusers met the inclusion and exclusion criteria.

4.9.5.4 Evidence statements

No evidence was identified.

4.9.5.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. Relapse, changes in the signs and symptoms of TB, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of tuberculosis.
Trade-off between benefits and harms	No evidence comparing the effectiveness of different antituberculosis regimens in patients who are substance misusers was identified. However, the group noted that the treatment of tuberculosis can be more difficult in patients who currently or have previously misused drugs or alcohol – for example, due to complications such as liver disease or because of interactions between the substances used and the antituberculosis

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	chemotherapy. For these reasons, those who currently or have previously misused drugs or alcohol can be at risk for poorer treatment outcomes – including treatmenmt failure, trelapse or the development of drug resistance – compared to those who do not or have not previously misused drugs or alcohol. The lack of evidence coupled with the GDG's awareness of these potential complications meant that they felt that patients with a history of substance misuse should be managed in conjunction with a specialist multidisciplinary team with experience of managing TB and substance misuse.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	No evidence comparing the effectiveness of different antituberculosis regimens in patients who are substance misusers was identified. The interaction studies informing the BNF and the SPCs for the first-line antituberculosis drugs were performed only in adults.
Other considerations	The BNF and SPCs for the first-line antituberculosis drugs recommend that doses may need to be modified in patients with a history of substance misuse. Patients should abstain from alcohol while receiving treatment due to an increased risk of hepatotoxicity. The need for caution is particularly highlighted for patients with alcohol dependence, and the use of these drugs should be carefully monitored with liver function tests and blood counts in these patients. Alcohol dependence is noted as a risk factor for isoniazid-associated peripheral neuropathy, and patients with a history of alcohol abuse should therefore receive prophylactic pyridoxine when taking isoniazid. Regular neurological examination is also advised. The use of some antituberculosis drugs is contraindicated completely in patients with drug-induced liver disease. The GDG felt that the lack of evidence, as well as the severity of the potential consequences of mismanagement, make specialist input essential in the treatment of tuberculosis in patients with a history of substance misuse.

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4.9.5.6 Recommendations

See section 4.9.1.6

4.9.5.7 Research recommendations

See section 4.9.1.7

4.9.6 People with tuberculosis and impaired vision or eye disease

4.9.6.1 Clinical introduction

Achieving adequate treatment of tuberculosis can be more difficult in patients who also have impaired vision or eye disease since some antituberculosis drugs are associated with an increased risk of visual deterioration. This evidence review focused on how the standard combination of antituberculosis drugs can be adapted to accommodate coexisting eye disease or impaired vision.

4.9.6.2 Review question

How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB?

4.9.6.3 Evidence review

As for the review in people coinfected with HIV, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all relevant papers. Randomised, quasi-randomised and non-randomised controlled trials, as well as prospective cohort studies, comparing different treatment regimens for TB in patients with active, drug susceptible TB and coexisting eye disease or impaired vision were considered for inclusion. (See Appendix C for the full review protocol). Exclusion criteria were as above for the review in people coinfected with HIV.

From a database of 3838 abstracts, 218 full-text articles were ordered, which covered all 7 comorbidities or co-existing conditions of interest, but no papers relating to the treatment of TB in people with coexisting eye disease or impaired vision met the inclusion and exclusion criteria.

4.9.6.4 Evidence statements

No evidence was identified.

4.9.6.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. Relapse, changes in the signs and symptoms of tuberculosis, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of tuberculosis.
Trade-off between benefits and harms	No evidence comparing the effectiveness of different antituberculosis regimens in patients with eye disease or impaired vision was identified. However, the group noted that the similar adverse effect profiles of antituberculosis drugs and eye disease, such as the potential for visual impairment associated with ethambutol, means that treatment of tuberculosis in patients with pre-existing eye disease or visual impairment should be managed in conjunction with a specialist multidisciplinary team with experience of managing TB and diabetes.
Trade-off between	None identified.

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net health benefits and resource use	
Quality of evidence	No evidence comparing the effectiveness of different antituberculosis regimens in patients with eye disease or impaired vision was identified. The interaction studies informing the BNF and the SPCs for the first-line antituberculosis drugs were performed only in adults.
Other considerations	The BNF and SPCs for isoniazid highlight the increased risk of optic neuropathy associated with the drug, which may further contribute to pre-existing visual impairment or disease. For this reason, patients receiving isoniazid should be given prophylactic pyridoxine. Additionally, the use of ethambutol is associated with a range of visual disturbances, including loss of acuity, restriction of visual fields, red-green colour blindness and optic neuritis. Care is therefore advised when ethambutol is prescribed to those with visual defects. Ocular examinations including acuity, colour discrimination and visual field are recommended before starting treatment and periodically during treatment, especially if high doses are used. Patients who cannot understand warnings about visual side effects should, if possible, be given an alternative drug; in particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately. The GDG felt that the lack of evidence, as well as the severity of the potential consequences of mismanagement, make specialist input essential in the treatment of tuberculosis in patients with eye disease or impaired vision.

4.9.6.6 Recommendations

See section 4.9.1.6

4.9.6.7 Research recommendations

See section 4.9.1.7

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4.9.7 People with tuberculosis who are pregnant or breastfeeding

4.9.7.1 Clinical introduction

As with many pharmaceuticals, concerns over the safety of antituberculosis drugs taken by women who are pregnant or breastfeeding. This evidence review focused on how the standard combination of antituberculosis drugs can be adapted to accommodate those who are pregnant or breastfeeding.

4.9.7.2 Review question

How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB?

4.9.7.3 Evidence review

As for the review in people coinfected with HIV, papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all relevant papers. Randomised, quasi-randomised and non-randomised controlled trials, as well as prospective cohort studies, comparing different treatment regimens for TB in patients with active, drug susceptible TB and who are pregnant or breastfeeding were considered for inclusion. (See Appendix C for the full review protocol). Exclusion criteria were as above for the review in people coinfected with HIV.

From a database of 3838 abstracts, 218 full-text articles were ordered, which covered all 7 comorbidities or co-existing conditions of interest, but no papers relating to the treatment of TB in people who are pregnant or breastfeeding met the inclusion and exclusion criteria.

4.9.7.4 Evidence statements

No evidence was identified.

4.9.7.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that mortality, cure (encompassing treatment success and treatment failure), and adverse events that are severe enough to require a modification, interruption or discontinuation of treatment were critical for decision-making. Relapse, changes in the signs and symptoms of tuberculosis, adherence to treatment and the emergence of acquired drug resistance were considered important for decision-making, but not critical. Although 'response to treatment' was not a predefined outcome of interest, it was considered to be a useful substitute for treatment success and failure, or changes in the signs and symptoms of tuberculosis.
Trade-off between benefits and harms	No evidence comparing the effectiveness of different antituberculosis regimens in patients who are pregnant or breastfeeding was identified. The group felt that the potential risks associated with firstline antituberculosis drugs to mother and foetus are generally outweighed by the benefits of treatment, noting the exception of streptomycin which should be avoided in pregnancy. Despite this, they felt that specialist management was advisable, particularly as a means of reassurance, which they hoped would both ease the stress of treatment upon expectant mothers and improve the likelihood of treatment adherence.
Trade-off between net health benefits	None identified.

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and resource use	
Quality of evidence	No evidence comparing the effectiveness of different antituberculosis regimens in patients who are pregnant or breastfeeding was identified.
Other considerations	The BNF and SPCs note that pregnancy is a risk factor for isoniazid-associated peripheral neuropathy, and patients who are pregnant should therefore receive prophylactic pyridoxine when taking isoniazid. Additionally, since isoniazid is excreted in breast milk, there is a risk of neuropathy in breastfed infants whose mothers are taking isoniazid; therefore they should be monitored for early signs of these effects and consideration should be given to treating the infant prophylactically with pyridoxine. The use of rifampicin in pregnant women in the third trimester is associated with an elevated risk of neonatal bleeding, and very high doses of rifampicin in first trimester have been associated with malformations of the foetus in animal studies. The GDG felt that the lack of evidence, as well as the severity of the potential consequences of mismanagement, make specialist input essential in the treatment of tuberculosis in patients who are pregnant or breastfeeding.

4.9.7.6 Recommendations

See section 4.9.1.6

4.9.7.7 Research recommendations

See section 4.9.1.7

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4.10 Treatment interruptions

4.10.1.1 Clinical introduction

Ensuring continuity in treatment and that adequate antituberculosis drugs are taken is key to successfully treating patients with tuberculosis. However, treatment interruptions are common and can have harmful consequences, both from the perspective of the individual (for example, through treatment failure or relapse) and from the perspective of the wider population (such as through prolonged infectiousness and increased transmission rates, as well as through the emergence of drug resistance).

Interruptions are most commonly due to the adverse effects of treatment or to poor adherence to regimens. Possible approaches to re-establishing appropriate treatment include extending the overall duration of treatment and restarting the treatment regimen from the beginning. In the case of interruptions arising following adverse events, approaches also include the concurrent reintroduction of drugs or the sequential reintroduction of drugs.

This review aimed to establish the most effective approach to re-establishing treatment for active tuberculosis following an interruption to treatment.

4.10.1.2 Review question

For people receiving drug treatment for active tuberculosis who experience treatment interruptions, what approach to re-establishing appropriate treatment is the most effective in reducing mortality and morbidity?

4.10.1.3 Evidence review

For this review question, papers were identified from a number of different databases (Embase, Medline, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database). A focused search strategy was used to pull in all studies that examined approaches to re-establishing appropriate antituberculosis treatment in people with active tuberculosis who have experienced treatment interruptions. Randomised, quasi-randomised and non-randomised controlled trials were considered for inclusion, as were cohort studies and case-control studies. Trials were excluded if:

- patients did not have a diagnosis of active tuberculosis;
- the study considered the use of drugs not licensed in the UK;
- the study design was that of a case study, case series or narrative review.

From a database of 7640 abstracts, 40 full-text articles were ordered and 2 randomised controlled trials met the inclusion criteria. Relevant data were extracted into evidence tables (see Appendix D). Where possible, the reviewer used Review Manager to meta-analyse the data into pooled effect estimates. GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E).

The included studies only reported data for the recurrence of hepatotoxicity and cure; none of the other outcomes specified in the review protocol (see Appendix C) were reported.

4.10.1.4 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 1610 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

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4.10.1.51 Evidence statements

Very low quality of evidence from 2 randomised controlled trial in 220 people with active tuberculosis who had experienced drug-induced hepatotoxicity showed sequential reintroduction of antituberculosis drugs to be associated with a lower recurrence of drug-induced hepatotoxicity than simultaneous reintroduction, though the effect was not statistically significant (OR (95% CI) = 0.44 (0.18 to 1.03)).

4.10.1.67 Evidence to recommendations

Relative value of different outcomes	With regards to reintroducing antituberculosis chemotherapy after a treatment interruption that occurred due to treatment-related adverse events, the GDG felt that the occurrence of adverse events, mortality and cure (including treatment success or treatment failure) were the most critical outcomes to decision making. Changes in the signs and symptoms of the disease, relapse, adherence or treatment default, and the emergence of acquired drug resistance were also considered important for decision-making, though these outcomes were not considered critical. Data was identified for the recurrence of hepatotoxicity and cure only. No data was identified for any of the other outcomes listed above. No evidence was found for the reintroduction of antituberculosis chemotherapy after treatment interruptions arising due to poor adherence.
Trade-off between benefits and harms	The GDG discussed what they felt constituted a clinically meaningful interruption to treatment and defined it as break in treatment for 2 weeks or more in the initial phase, or more than 20% of prescribed doses missed intermittently throughout the regimens. The GDG noted the limited availability of data for the reintroduction of antituberculosis chemotherapy after adverse events, for which evidence was only available for drug-induced hepatotoxicity, as well as the absence of any data for the reintroduction of chemotherapy following poor adherence. The GDG felt that the paucity of data was noteworthy, and that further data would have been useful to their decision-making. No paediatric evidence was identified, although the group also noted that drug-induced hepatotoxicity is not a common event in children. Recommendations for the management of poor adherence were primarily based on the reviews found in chapters 9.1 and 9.2. Theoretically, the approach to re-establishing treatment may vary depending on the duration of the interruption or the proportion of doses missed and the bacillary load of the patient, which is in turn dependent on whether the interruption occurred during the initial or the continuation phase of therapy (due to a higher bacillary load during the initial phase), and the patient's smear status (due to the higher bacillary load inherently present in smear-positive patients). Longer interruptions, those that include a higher proportion of missed doses, and/or those that occur earlier in the course of treatment may require restarting treatment from the beginning. However, the lack of evidence meant that the group felt unable to make recommendations that involved this level of detail. In terms of responding to an episode of drug-induced hepatotoxicity, there is a balance between the need for adequate, continuous treatment, which is essential to prevent treatment failure, relapse or the emergence of drug resistance, with the risk of continuing treatment. The group felt that antituberculosis regimen should be stopped immediately due to the potentially severe consequences of a prolonged reaction. The group also noted, however, that not all hepatotoxic reactions are caused by antituberculosis chemotherapy. Investigation to rule out other causes of abnormal liver function, such as concurrent drug or alcohol use or viral hepatitis, was therefore considered to be important. Once liver function stabilises, it is important that treatment resumes. The GDG observed that the reintroduction of antituberculosis drugs sequentially appeared to be associated a reduced recurrence of hepatotoxicity compared to a reintroduction

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	of all drugs simultaneously. This reflected the experiences of the group, and therefore they felt that sequential reintroduction should be used over simultaneous reintroduction in people who have experienced drug-induced hepatotoxicity. Hepatotoxicity may be caused by many drugs, therefore sequential reintroduction can help to pinpoint which drugs are causing the problem. Ethambutol is the least likely cause of hepatotoxicity, therefore it was felt that it should be reintroduced first. Since monotherapy is not advised in the treatment of active tuberculosis due to the potential risk of treatment failure, relapse or for the emergence of drug resistance, the group emphasized that ethambutol's reintroduction should be accompanied by that of another antituberculosis drug. In patients in whom the disease is severe or who are thought to be particularly infectious, the group felt that the use of quinolones may be justified – either in the short term while attempting reintroduction of standard agents, or as part of a new regimen. The GDG felt that isoniazid or rifampicin is still appropriate in those who do not have severe disease or who are not thought to be infectious. The group discussed other adverse events that can occur during antituberculosis chemotherapy and which may lead to treatment interruptions, and felt that cutaneous reactions were also an area of concern. However, they felt that for a treatment interruption to be justifiable, a cutaneous reaction needed to be acute and/or significant. Many cutaneous reactions to antituberculosis chemotherapy will not warrant an interruption to treatment. As was the case of hepatotoxicity, ethambutol is less likely to cause the reaction and should therefore be considered for reintroduction first. Pyrazinamide is the most likely cause[ee], and reintroduction should be avoided. Again, the risks of monotherapy were noted, and the group stressed the importance of reintroducing ethambutol alongside another antituberculosis drug. The absence of any evidence for the management of treatment interruptions in those who have experienced drug-induced cutaneous reactions meant that the group felt the involvement of a dermatologist should be recommended.
Trade-off between net health benefits and resource use	No health economic evidence was found in the literature search for this question. This, combined with the issues raised in the "Quality of Evidence" section below, meant that the GDG was unable to explore trade-offs between net health benefits and resource use.
Quality of evidence	Due to the limited availability of evidence, the recommendations for the reintroduction of antituberculosis chemotherapy after adverse events were largely consensus-based, using the clinical experience of the GDG and additional input and expertise from a pharmaceutical adviser. Recommendations for the management of poor adherence were therefore based on the reviews found in section 9. The GDG felt that this area would benefit considerably from further evidence. In terms of re-establishing treatment following drug-induced hepatotoxicity, evidence was identified for the recurrence of hepatotoxicity and cure only. No data was identified for any of the other outcomes listed above, which the GDG felt may have assisted their decision-making. No paediatric evidence was identified. The overall quality of the data for each outcome was very low. The small sample sizes and low event rates meant that the effect estimates were very imprecise. Poor reporting were common in the identified evidence, including failure to describe methods of randomisation and the use of allocation concealment and blinding, as well as the duration of follow-up used.
Other considerations	None.

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[ee] Ormerod LP and Horsfield N (1995) Frequency and type of reactions to antituberculosis drugs. *Tubercle and Lung Dise*ase 77: 37-42

4.10.1.7 Recommendations

81. In people who have experienced a treatment interruption because of drug-induced hepatotoxicity:

- investigate other causes of acute liver reactions
- wait until aspartate or alanine transaminase levels fall below twice the upper limit of normal, bilirubin levels return to the normal range and hepatotoxic symptoms have resolved, then
- sequentially reintroduce each of the anti-TB drugs over a period of no more than 10 days, starting with ethambutol and either isoniazid or rifampicin. **[new 2015]**

82. In people with severe or highly infectious TB who need to interrupt standard therapy because of a reaction, consider continuing treatment with:

- for hepatotoxicity, a combination of at least 2 anti-TB drugs of low hepatotoxicity (such as ethambutol and streptomycin, with or without a quinolone, such as levofloxacin or moxifloxacin) and monitor with a liver specialist for further reactions
- for a cutaneous reaction, a combination of at least 2 anti-TB drugs with a low risk of cutaneous reactions (such as ethambutol and streptomycin) and monitor with a dermatologist for further reactions. [new 2015]

83. If another reaction of a similar or greater severity occurs because of reintroducing a particular drug, exclude that drug from future regimens and consider extending the total regimen accordingly. [new 2015]

4.10.1.8 Research recommendations

8. For people with active, drug susceptible TB who experience treatment interruptions because of adverse events, particularly hepatotoxicity, what approach to re-establishing treatment is most effective in reducing mortality and morbidity?

Why this is important

There is little evidence on re-establishing treatment after interruptions because of adverse events. This is key to ensuring treatment success without relapse or the emergence of drug resistance, but avoiding of further adverse events is also important. Randomised controlled trials are needed to compare approaches to re-establishing treatment for active, drug susceptible TB after it is interrupted because of adverse events, particularly hepatotoxicity. These trials should assess mortality, treatment success or failure, rates of relapse, the recurrence of adverse events and the emergence of drug resistance. Approaches evaluated could compare, for example, restarting regimens with lengthening their duration, as well as sequential reintroduction. Approaches should vary depending on the proportion of doses missed and the stage of treatment (initial or continuation phase) in which the interruption occurred. Prospective observational cohort studies with multivariable analyses may also be useful.

9. What are the costs of adverse events, particularly hepatotoxicity, in people who are undergoing treatment for TB, including effects on quality of life?

Why this is important

The health economists for this guidance were unable to identify reliable data on how adverse events affected quality of life and costs in people being treated for TB. Such

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data are essential in producing economic models that reflect the real costs of treatment. Data need to be collected and reported on the quality of life and other costs of adverse events, particularly hepatotoxicity, experienced by people being treated for TB.

10. Combine data from different national and local registries to improve data use.

Why this is important

There are gaps in the evidence base for several areas of the guideline. These include the best approach to re-establishing treatment after an interruption and the optimal duration of isolation for infection control. The Committee acknowledged that there are excellent sources of information available - such as cohort review databases, the London TB database and the national Enhanced TB Surveillance System database - but these are not linked in any way. A study group with access to these registries and databases could focus on identifying people who have:

- experienced treatment interruptions, and link the management approach to outcomes such as mortality, treatment failure, relapse and drug resistance, as well as to costs; or
- undergone isolation, and link the duration of isolation to TB infection rates, treatment outcomes, measures of quality of life and costs.

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4.11 Treatment completion and follow-up

4.11.1 Clinical introduction

In the UK, when the recommended regimen has been given to patients with fully susceptible organisms, the rate of relapse is low (0–3%) in both trial and clinical practice conditions, if there has been good adherence with treatment. Under these circumstances, it is important to know whether routine follow-up after treatment completion is cost-effective in detecting relapse.

4.11.2 Methodological introduction

No studies were identified which compared the detected relapse rates of previously treated TB patients who were subject to routine follow-up, with a group who did not receive routine follow-up.

However, there were five case series which reported the proportion of relapsing patients who were identified as a relapse case during routine follow-up appointments and the number of cases who self-referred outside routine follow-up due to onset of symptoms or who were referred by their general practitioner (GP) or detected after an admission for another initial diagnosis. Two studies were conducted in the UK, two in the USA and one in India.

Many of the studies found were performed 20 to 30 years ago, prior to the advent of modern treatment regimens. These studies generally concluded that routine follow-up was unnecessary, which may explain the dearth of studies on routine follow-up for previously treated TB patients since this time. In addition, the definition of relapse varied across studies and in all the studies (apart from one where it is not clear) only patients with pulmonary TB were included.

4.11.3 Evidence statements

Detection by routine follow-up

In five case series studies of previously treated TB patients found to have relapsed, the percentage detected at routine follow-up clinic attendances were 27%, 35%, 40%, 51% and 58% (one study only included patients who had completed treatment). **(3)**

One study calculated that routine surveillance of 1,000 patients who had completed treatment would help to identify approximately six relapses in one year whilst a yield of 0.6% of relapse cases detected from routine follow-up was calculated in another study. **(3)**

Rate of relapse

In a UK study the relapse rate at five years since the start of treatment was 3.5%. In another study 4% of patients with active TB added to a TB register over a 7.5-year period had been diagnosed with reactivated disease whilst in the Indian study the authors calculated a cumulative relapse rate of 11.6% at five years in patients who completed treatment. **(3)**

Risk factors for relapse

Of the patients who relapsed in a UK study, 82% discharged themselves prematurely from hospital and/or terminated their own treatment. In another study 75% of relapsed patients over a 7.5-year period had a combined treatment regimen which was self-interrupted or self-discontinued and a further 14% received no treatment or streptomycin only. An Indian study found the main reason for prolongation of treatment was irregular drug taking during the course of treatment. Patients who completed their course of treatment in less than 24 months

had an overall relapse rate of 4.09 % in five years; those who required 24 to 30 months had a cumulative relapse rate of 10.85% ($p<0.05$). **(3)**

In a group of relapsed chronic sputum-positive patients, 57% had inadequate duration of treatment regimen (less than 18 months) and a further 23% had adequate duration but irregular treatment. In another study 61% of relapsed patients were not treated for the recommended treatment duration of 18 months. Of a group of relapsed patients detected during routine follow-up, 49% had inadequate treatment (<1 year) with an effective regimen, or interruption of treatment serious enough to make the possibility of at least one year of continuous treatment unlikely. Of these relapsed patients, 94% were found to have 'complicating factors' which included inadequate therapy, alcoholism or poor cooperation. **(3)**

In one study the relapse rate in men was nearly twice that in women and was also higher in patients over 45 years. The relapse rate did not seem to be related to the extent of the disease. In another study of treatment completion patients the cumulative five-year relapse rate did not differ significantly between men and women or in terms of age or extent of initial disease, initial cavitary status or presence of drug-resistant bacilli. **(3)**

The mean time between last positive sputum smear and relapse in patients treated after 1955 (when adequate therapy was employed) was 7.5±4.88 years. **(3)**

4.11.4 From evidence to recommendations

All patients should receive 'inform and advise' information upon treatment completion. They should then inform other healthcare professionals, who may provide or organise their care in the future, of their history of latent TB or disease.

Routine follow-up was felt to be necessary for MDR TB, and worth considering for isoniazid-resistant TB, because these patients have received non-standard treatment with a potentially higher relapse rate.

The GDG felt that regular follow-up clinic visits were unnecessary. Patients should be advised to be alert to symptoms and to contact the TB service rapidly.

4.11.5 Recommendations

84. Follow-up clinic visits should not be conducted routinely after treatment completion. [2006]

85. Tell patients to watch for symptoms of relapse and how to contact the TB service rapidly through primary care or a TB clinic. Key workers should ensure that patients at increased risk of relapse are particularly well informed about symptoms. [2006]

86. Patients who have had drug-resistant TB should be considered for follow-up for 12 months after completing treatment. Patients who have had multidrug-resistant TB should be considered for prolonged follow-up. [2006]

5 Drug-resistant TB

5.1 General principles for management strategies for drug-resistant tuberculosis – position paper

5.1.1 Clinical introduction

The management of drug-resistant tuberculosis is relevant to both personal and public health, both in terms of the approaches to management and their implications. Further complicating features include:

- drug resistance which is suspected compared to that which is known;
- the different implications of method used to identify drug resistance (for example, a molecular test indicating genotypic rifampicin resistance will prompt further testing, such as for isoniazid resistance, and a probable switch to/start of treatment for multidrug-resisant tuberculosis pending other information, whereas culture-based drug susceptibility allows upfront initiation of a likely appropriate regimen).

5.1.2 Review question

What management strategies are most effective for managing all cases of drug-resistant TB?

5.1.3 Position paper

5.1.3.1 Introduction

Due to the lack of evidence available to address this question, the GDG felt that this review question would be best answered by drafting a position paper on the current state of practice in the UK would be the most appropriate resource for answering this question.

5.1.3.2 Question(s)

Outline the following:

- the current situation;
- the management strategies you have found most effective in practice and why;
- how to decide which management strategy to use;
- the key things that should be considered and the decision making process;
- areas of uncertainty.

5.1.3.3 Authors

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5.1.3.41 Position

5.1.3.4.12 Current UK practice

3 *Diagnosis*

4 This mainly relies on phenotypic drug susceptibility testing – that is, culture-based – from
5 reference laboratories. Due to the time taken to perdorm culture-based drug susceptibility
6 testing, results often arrive late and mostly after some kind of initial treatment regimens have
7 been started. The delay means that there is a risk of longer periods of infectivity or ongoing
8 transmission, and a risk that additional drug resistance may develop in patients who have
9 been started on an inappropriate regimen.

10 Current diagnostic strategy is therefore:

11 • to obtain as much material for mycobacterial culture as possible, before starting treatment
12 to avoid interference;
13 • to ask, where this is possible and as soon as possible, for molecular resistance testing in
14 patients who are at an increased risk for drug resistance (in practice, this is for isoniazid
15 and rifampicin only);
16 • to take the positive predictive value of the molecular test result into consideration,
17 particularly if the prior probability of drug resistance is either low or difficult to judge; this is
18 in order to avoid switching treatment regimens an unnecessary number of times, as can
19 happen when, for example, initial molecular tests indicated isoniazid and rifampicin
20 resistance but the culture-based drug susceptibility testing later show a patient to have
21 fully sensitive disease.

22 *Isolation*

23 In practice, there is some uncertainty about whether all cases of drug resistant tuberculosis
24 need isolation while in hospital, or if it is only those with multidrug resistance. Additionally,
25 what should be done before the results of drug susceptibility testing are known? Should it
26 only be sputum smear positive cases? Should it be all pulmonary cases? Should isolation
27 always be in negative pressure rooms?

28 Current isolation strategy is:

29 • to isolate all sputum smear positive cases in negative pressure rooms, regardless of
30 resistance;
31 • to find ways of avoiding cabin-fever in those who are going to need prolonged isolation
32 (such as people with multidrug or extremely resistant tuberculosis) – for example,
33 planning walks to the park, providing internet access or enabling telephone conversations.

34 *Choice of drug regimen*

35 Choice of regimen should be guided by the results of drug susceptability testing. Treatment
36 guidelines from the World Health Organization are generally followed for multidrug or
37 extremely resistant tuberculosis, though specialist input remains key. Furthermore, current
38 practice is increasingly moving towards the use of regimens for multidrug resistant
39 tuberculosis in patients with isolated rifampicin resistance, with the amendment that isoniazid
40 is retained. How to manage other combinations of resistance is considered on a case-by-
41 case basis with specialist input. In particular, clinicians should discuss appropriate
42 management options with the British Thoracic Society MDR-TB Advisory Network.

43 *Adherence*

44 Directly observed therapy is advocated for all drug-resistant cases, regardless of resistance
45 pattern. Video-based supervision has been useful in some cases, particularly in those on
46 longer regimens.

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There is also a need to link patients to support mechanisms, such as patient support groups.

Monitoring and follow-up

Intensive monitoring and follow-up of treatment in those with multidrug resistant disease is important due to the complexity of treatment, the high 'cost' of failure, and the risk of adverse events. Discussion at regional multidrug resistant tuberculosis team meetings within local clinical networks can be one way to promote this.

Confirming cure

Evidence of culture negativity is heavily relied upon, but it is important to note that there can be problems with this. For example, when the initial culture is negative and only a molecular test was available, or when a follow-up culture fails or is not possible because of inability to obtain a specimen. Because of the difficulty in documenting cure with certainty, it is common for patients with multidrug resistant tuberculosis to be followed up for prolonged periods of 5 years or more.

Contact tracing and choice of chemoprophylactic regimens

Where the index case has multidrug resistant tuberculosis, contact-tracing is a priority.

For patients with latent tuberculosis infection for whom the index case is not suspected to have multidrug resistant tuberculosis, the chemoprophylactic regimen is tailored to the resistance pattern of the isolate from the index case. For isoniazid monoresistance, 4 to 6 months of rifampicin is commonly used. Where the index case has multidrug resistant tuberculosis, the regimen may be designed based on the resistance pattern of the isolate from the index case, though chemoprophylaxis is not always given.

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5.1.3.5 Most effective management strategies

Information on risk factors for drug resistance should be prospectively collected to inform practice (including factors such as known residence or birth in a country with high rates of drug resistance, time in prison, exposure to a known or suspected case of drug resistance tuberculosis, previous treatment for tuberculosis).

Send as much material for culture as possible, before starting treatment; culture should be performed both on isolates of the *M. tuberculosis* complex, as well as directly on primary specimens.

If resistance to isoniazid and/or rifampicin is detected, additional susceptibility testing should be pursued. This may include testing for susceptibility to ethambutol, aminoglycosides or cyclic peptides, and fluoroquinolones.

Genotypic susceptibility testing should be performed in all patients at risk of multidrug resistance.

Faster recognition of drug resistant cases and earlier use of an appropriate regimen will:

- reduce the overall duration of treatment, particularly in patients with isoniazid monoresistant tuberculosis;
- potentially reduce the duration for which patients' may pose a risk of infectivity;
- potentially reduce the risk of transmission in 'all' cases;
- reduce use of ineffective agents and the unnecessary risk of adverse effects that these pose.

All patients with suspected or confirmed resistance should undergo rapid assessment for their risk of infectiousness to others, and appropriate infection control measures initiated.

Health care workers and others in contact with patients with pulmonary, or 'infectious', tuberculosis should use appropriate infection control measures, such as FFP3 masks, to protect themselves against transmission until drug susceptibility is demonstrated.

The management of all cases with suspected or confirmed resistance should be discussed amogst a multidisciplinary team with experience of managing drug resistant tuberculosis, including registration on the BTS Advice Line.

Directly observed therapy should be used for the drug treatment of all people with drug resistant tuverculosis, though should there should be flexibility in how this is delivered (for example, the use of video-based supervision).

5.1.3.6 How to decide which management strategy to use

The most intensive strategies should be focussed on patients in the most difficult circumstances. It might need only one or two of the below strategies for some patients, but a wider combination for those with difficult social circumstances or co-morbidities.

Things to consider:

- Are there any identifiable risk factors for drug resistance, particularly multidrug resistance? These might include:
  - ethnic origin or country of birth, using international surveillance data on drug resistance from the World Health Organization as a guide;
  - known contact with known case of drug resistant TB;
  - history of previous TB;
  - history of treatment, including that for drug sensitive TB: are there any known concerns about adherence to that treatment, any risk of significant adverse events or drug-drug interactions with proposed drug regimen, or any reason to sus[pect that a patient may not respond as expected?

  It should be noted, however, that this can still be unreliable; it is not uncommon for multidrug resistance to be found in patients with no identifiable higher risk factors at the time of initial assessment.
- What is the perceived infectiousness of patient? Factors to consider may include:
  - the suspected site(s) of disease;
  - if pulmonary, is there:
    - coughing
    - cavitation on the chest x-ray
    - smear positivity
- What is the clinical condition of patient, the site of disease and is there a need for early, effective treatment?

5.1.3.7 Areas of uncertainty

How to determine who should be regarded as at risk before results are available. This impacts on:

- determining the positive predictive value of molecular tests;
- deciding which patients to isolate and at what level of isolation; conversely, how quickly can patients who are in isolation be de-isolated (including discharged home)? What are the criteria for de-isolation? Is smear status for pulmonary TB too insensitive a marker of infection (and hence onward transmission to others)?

Which regimen to start, considering the risk of further resistance on sub-optimal treatment.

Whether there can be a greater use of FFP3 masks, considering:

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- expense;
- acceptability to healthcare wprkers;
- stigmatisation of patient.

Cost- and clinical effectiveness of less restricted use of genotypic testing (current practice is generally for pulmonary or critical disease sites only). However, there is also a risk to the patient of 'falsely' suspecting multidrug resistance and the patient being switched to a less effective regimen in the interim.

5.1.48 Evidence to recommendations

Relative value of different outcomes	Not applicable.
Trade-off between benefits and harms	The GDG discussed the position paper drafted on the management strategies that are considered to be effective in the management of patients of drug-resistant TB. Although they felt it was informative, they did not feel it was sufficient grounds on which to produce recommendations. The only exception was the consensus-based recommendation regarding actions to improve the quality of life for patients during prolonged isolation due to suspected or confirmed drug resistance. The group felt that this was important, and had witnessed the benefits of such efforts in their own practice, despite having found no evidence for it.
Trade-off between net health benefits and resource use	Inpatient isolation is a high-cost intervention for preventing the onward transmission of infectious TB. In addition to this cost, the GDG recognised that the quality of life implications of inpatient isolation are likely to be significant, but as yet remain poorly quantified and are often overlooked (see appendix F). Given the absence of relevant evidence, the GDG drew on their own clinical experience in determining that these recomendations, which include interventions which have a very low cost attached, would represent good value in attenuating some of the detrimental impacts on the individual being isolated.
Quality of evidence	The GDG noted the consensus status of this position paper and agreed quality of evidence was very low
Other considerations	None.

Update 2015

5.1.50 Recommendations

87. As soon as possible, explore options to reduce the psychosocial impact of prolonged isolation. For example, through providing free access to Internet, telephone and television, and accompanied walks in the open air. [new 2015]

5.2 Risk factors for drug resistance

5.2.1 Clinical introduction

Drug resistance is an important issue in the management of tuberculosis. It threatens the progress made in tuberculosis care and control worldwide because it may prolong the period during which patients are infectious to others, as well as compromising the effectiveness of treatment.

Resistance to particular single drugs develops in individual bacteria by natural mutations in between one in 10^5 and one in 10^7 organisms[ff], depending upon the drug in question. Multiple drug combinations overcome this problem provided enough drugs are given and taken correctly, but modification of the treatment may be required. Cases of treatment failure have a high chance of having developed acquired drug resistance, which can be rapidly assessed with molecular probes for rifampicin resistance and a repeat drug susceptibility profile. Resistance to antituberculosis drugs is defined as a level of resistance to four times or greater the concentration of drug required to inhibit a fully susceptible organism.

Resistance can be acquired, in a patient with a fully susceptible organism, by inadequate drug treatment being prescribed and/or inadequate adherence to treatment. Resistance can be also be primary, with a patient being infected with an already drug-resistant organism, thus having drug resistance without a prior treatment history. Resistance can be to a single drug, for example mono-resistance to isoniazid, or to multiple drugs, for example to both isoniazid and streptomycin. Multidrug resistant tuberculosis is defined as resistance to at least isoniazid and rifampicin, with or without resistance to other drugs.

Multidrug resistant tuberculosis is particularly concerning as there is loss of both the main bactericidal drug (isoniazid) and the main sterilising drug (rifampicin). The consequences of this situation are considerable. Such patients who are sputum smear positive remain infectious for much longer than those with susceptible organisms, have a higher death rate from, and a lower cure rate for, their tuberculosis. Multidrug resistant tuberculosis requires individualised complex regimens, which themselves require a greater degree of specialist input, as well as multiple reserve drugs of higher toxicity. Consequently, this type of disease is far more expensive to treat and places are far greater burden on the patient.

Drug resistant disease can occur in anyone, but there are a few groups who are more heavily affected. According to the 2013 UK data from Public Health England, resistance is more prevalent in those with a previous history of tuberculosis and those with social risk factors, in particular those reporting drug misuse or imprisonment. The proportion of cases with isoniazid resistance – the most common form of resistance – is higher in the non-UK born compared to those born in the UK, with the highest number of cases in those born in India, Pakistan and Somalia, but the highest proportions of cases in those born in Ireland, Lithuania, the Ukraine and Eritrea. In the case of multidrug resistant tuberculosis, the majority of patients were also born outside the UK, with the highest number of cases from India, Pakistan and Somalia, and the highest proportions in those from the Ukraine, Lithuania, Latvia and Sierra Leone.

This review aimed to establish which risk factors are associated with drug-resistant tuberculosis in the UK, and which may form a useful screen for initiating rapid drug susceptibility testing, or for whom infection control measures and treatment appropriate to drug resistant disease should be initiated.

Update 2015

[ff] David HL and Newman CM (1971) Some observations on the genetics of isoniazid resistance in the tubercle bacilli. American Review of Respiratory Disease 104(4): 508-15

5.2.2 Review question

Which clinical signs and symptoms or risk factors are associated with a higher level of: i) multidrug resistance, or ii) any drug resistance in people with suspected or confirmed active tuberculosis in the UK?

5.2.3 Evidence review

For this review question, papers were identified from a number of different databases (Embase, Medline, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database). A focused search strategy was used to pull in all relevant prognostic studies on recent UK data. These were specified as full text papers examining clinical signs, symptoms or risk factors for i) multidrug resistance, or ii) any drug resistance in people with suspected or confirmed active tuberculosis in the UK. If insufficient evidence had been found, an analysis of national surveillance data for UK-specific risk factors would have been conducted. In addition to this, the most recent international surveillance data from the World Health Organisation was used to highlight countries with a high incidence of drug resistance.

Trials were excluded if they were:

- did not use multivariate analyses;
- formal diagnostic investigations to confirm drug resistance;
- case studies, case series and narrative reviews.

The review considered the evidence by type of resistance. Since studies that cover notified tuberculosis cases over the same time period will have included the same cases in their analyses, the most recent evidence with the largest sample size was selected.

From a database of 4405 abstracts, 235 full-text articles were ordered and 8 papers met the inclusion criteria.

All recommendations were made using those from the previous guideline (CG117) as a starting point.

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5.2.4 Health Economic Evidence

An economic evaluations filter was applied to the search protocol and 1610 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

5.2.5 Evidence statements

Risk factors for drug resistance

Very low quality evidence from 2 studies, with 614 participants, that examined the relationship between the development of TB drug resistance and variables (including age, sex, HIV status, previous history of tuberculosis, exposure to drug resitant tuberculosis, place of birth, ethnicity, imprisonment, homelessness) found that only previous history of tuberculosis (in 1 study), imprisonment and homelessness were statistically significant risk factors for the development of TB drug resistance

First line–drug resistance

Very low quality evidence from 1 study, with 104 participants, thet examined the relation between the development of first-line TB drug resistance and variables (including adherence,

previous history of tuberculosis, site of disease, place of birth, foreign travel, time in UK, found that only adherence and previous history of tuberculosis, were statistically significant risk factors for the development of first-line TB drug resistance

Risk factors for isoniazid resistance

Very low to low quality evidence from 6 studies, with 57777 participants, thet examined the relationship between the development of TB drug resistance and variables (including age, sex, HIV status, site of disease, smear status, previous history of tuberculosis, exposure to drug resitant tuberculosis, place of residence, place of birth, ethnicity, employment, problem drug use, asylum seeker/refugees, imprisonment, homelessness) found that only exposure to drug resistant TB, previous history of tuberculosis, London as place of residence, Black Caribbean ethnicity, unemployed, employed as drug dealer or sex worker, problem drug use, asylum seeker/refugee and imprisonment were statistically significant risk factors for the development of isoniazid resistance

Risk factors for rifampicin resistance

Low quality evidence from 1 study, with 28481 participants, thet examined the relationship between the development of TB drug resistance and variables (including age, sex, site of disease, previous history of tuberculosis, place of residence, place of birth, ethnicity) found that only previous history of tuberculosis and place of birth outside the UK were statistically significant risk factors for the development of rifampicin resistance

Risk factors for multidrug resistance

Very low to low quality evidence from 4 studies, with 55802 participants, thet examined the relationship between the development of TB drug resistance and variables (including age, sex, HIV status, site of disease, smear status, previous history of tuberculosis, place of residence, place of birth, ethnicity and, homelessness) found that only positive smear status in those with previous tuberculosis, pulmonary tuberculosis, HIV positive status in those with no previous tuberculosis, London as place of residence in those with no previous tuberculosis, Place of birth outside the Uk but resident in the UK for less than 5 years, ethnicity from Indian subcontinenet or black African and homelessness were statistically significant risk factors for the development of multidrug resistance

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5.2.60 Evidence to recommendations

Relative value of different outcomes	The group felt that that the outcomes of interest for this review were the risk of different drug resistance occurring amongst people with active tuberculosis in the UK.
Trade-off between benefits and harms	**Isoniazid resistant tuberculosis and other monoresistances** The group discussed the value of predicting monoresistances, in particular the most common, isoniazid mono-resistance. They noted that the standard recommended combination of drugs, isoniazid, rifampicin, pyrazinamide and ethambutol (link to Tx recs/chapter), was formulated with exactly such issues in mind. That is, should a single drug fail, treatment is still adequate due to coverage by the remaining 3 drugs. In this way, the use of rapid drug susceptibility testing, and subsequent adjustment of a treatment regimen, for monoresistance is not always urgent or necessary. It For patients with monoresistance, drug susceptibility testing by culture alone is likely to be generally suitable. is only if there was resistance to 2 or more antituberculosis drugs, then there is a risk that not all the bacteria will be killed and that the patient will experience treatment failure, relapse or that they will become resistant to those drugs. The group then discussed the scenario of a patient with, for example, isoniazid resistance who was experiencing isoniazid-associated adverse events. One course of action may be to remove the isoniazid from the regimen. However, the group felt such a decision would not be made based on a risk assessment alone,

rather it would be based on the results of diagnostic investigations for drug resistance. More than this, the group felt that it would generally be preferable to leave the isoniazid in the regimen even if resistance exists. This was because it allows the continued use of combination tablets, which is associated with a lower pill burden and also means less changes to the regimen and therefore less chance of the wrong or insufficient doses being used. It was felt that this had a greater potential for benefit than the harm of the potential isoniazid-associated adverse events, which are generally of low severity. The group felt that this bolstered their decision not to recommend a risk assessment for isoniazid monoresistance.

Multidrug resistant tuberculosis

The group felt that it was important to note that the absence of risk factors is not enough in itself to remove clinical suspicion of drug resistant tuberculosis.

In discussing the usefulness of different risk factors for multidrug resistant tuberculosis, the GDG defined the purpose of a risk factor profile in this context to be the initiation of rapid diagnostic investigations for multidrug resistance. In practice, this means a risk assessment for the initiation of rapid diagnostic NAATs for rifampicin resistance, which is considered a proxy for multidrug resistance.

The group noted that the most significant risk factors will be population-specific; that is, they will depend on the population within which a drug resistant strain is transmitted. For example, factors found to be valid for London may not be relevant to the whole of the UK. However, they did not find sufficient evidence upon which to make such a recommendation.

The group discussed age and sex as a risk factor for multidrug resistance, and noted that although there is a decreasing trend in this risk with age and female gender, they did not feel that the evidence was strong enough or of sufficient quality to make a recommendation. Additionally, the group did not feel comfortable having patients differentiated on the basis of their age or sex: the group did not want to discourage the investigation of older and/or male patients.

The group noted that the evidence for HIV positivity as a risk factor for multidrug resistance was conflicting. However, they had more confidence in effect estimate provided by the larger study, which held the additional benefit of examining more recent data. This study found that HIV positivity in people with tuberculosis was not associated with an increased risk of multidrug resistance. The group therefore felt that the evidence did not support the retention of HIV positivity in the risk assessment.

The group discussed ‘residence in London’ as a risk factor, and noted that although there was some evidence to suggest that this was associated with an increased risk of multidrug resistance amongst patients with no previous tuberculosis, the effect was not strong and the data was not recent (England and Wales 1993-4 and 1998-2000). Furthermore, this effect was not observed amongst patients who *did* have a history of tuberculosis. The group were also aware of more recent data from Public Health England that showed that residence in London was not associated with an increased risk of multidrug resistance. Therefore, they felt that the evidence did not support the retention of ‘residence in London’ in the risk assessment.

Homelessness appears to be associated with an increased risk of multidrug resistance amongst people with tuberculosis; however, this evidence came from a single study that examined only data from London (2004, n = 1540). The group did not feel there was sufficient evidence to add this factor into the risk assessment.

The group noted the paucity of evidence on the usefulness of ‘a history of tuberculosis’ as a risk factor for multidrug resistance. However, they did not feel that this constituted a basis on which to remove this factor from the risk assessment, particularly given that this had been a useful risk factor in their own experience, most prominently where there has been poor adherence to previous treatment. Furthermore, given that a known mechanism is the improper or insufficient treatment of tuberculosis, the retention of this risk factor also makes theoretical sense. This was further supported by the finding that there was a significantly higher risk of rifampicin resistance, a marker of probable multidrug resistance, among patients with a previous history of tuberculosis compared to

	those with no history of tuberculosis. The group also noted the lack of evidence for 'contact with a known case of multidrug resistant tuberculosis'. However, again, they did not feel that this constituted a basis on which to remove this factor from the risk assessment, as it had also been a useful risk factor in their own experience. The retention of this risk factor also makes theoretical sense in that if the index case from which a patient obtained the disease had multidrug resistance, then so too would the case in question. Birth or residence in a country with a high incidence multidrug resistance was also retained in the risk assessment. Again, the group did not have evidence to suggest that this factor should be removed, and it too had been a useful, rational risk factor in their experience. They chose to specify those countries with a high proportion of tuberculosis cases having multidrug resistance as reported by the World Health Organization, rather than specific countries, as this would allow 'future-proofing' of the guidance. A threshold of greater than or equal to 5% of new cases was devised by the GDG because it captures all countries with a high risk of multidrug resistance according to current global surveillance data. The group recognised that it would be preferable to have a more evidence-based threshold, but in lieu of this they felt that this limit had worked well in their experience. This risk factor was also supported by the evidence review in that those most affected by multidrug resistance were shown to be those from the Indian Subcontinent and black Africans, though this evidence was considered to be weak.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	The quality of evidence for each risk factor was appraised as low to very low. In many of the studies it is unclear if the measurement of the prognostic factor or outcome were blinded. Furthermore, many studies did not report which variables (e.g. ethnicity, place of residence) were controlled for in their multivariate analyses. Therefore, it is unclear if, or to what extent, other factors than the factor of interest were driving results. For example, those patients who are UK born are more likely have social risk factors for drug resistance, such as homelessness or drug misuse, and it may be these driving associations (or lack thereof) between birth in the UK and drug resistance. Additionally, the retrospective nature of many of these studies often means data about some risk factors is not recorded in detail or at all, so risk factor data may have been incomplete.. It should be noted that studies which cover notified TB cases over the same time period will have included the same cases in their analyses. Furthermore, all of the data examined was collected almost 10 years or more ago, limiting its applicability to the situation in the UK today
Other considerations	Consensus, and the experiences and practice of the GDG, were significant in the development of the recommendation as the evidence base was not considered strong. The group noted that much of the data was from 10 years or more ago. This limited the generalisability of the evidence to the UK today. Patterns of resistance, particularly those in non-outbreak situations, and migration patterns have changed considerably in the last 10-15 years. With regards migration patterns, this may be reflected in the ethnicity/place of birth data; for example, 'white' would encompass many Eastern European patients, when perhaps it would be more useful to decision-making if Eastern European patients were considered separately from Western European patients. Although 1 study showed a trend towards decreasing risk of multidrug resistance with increased age, the effect was nonsignificant and the summary estimate was given for age as a linear variable, which is not easy to operationalise into a recommendation. A second study showed people with tuberculosis aged 15 to 44 years were significantly more likely to have multidrug resistance than those aged

	45 to 64, or 65 and above, amongst patients with no previous history of tuberculosis. However, the group felt that the unmatched case-control design and the lack of information on which variables were controlled for in the multivariate analyses, as well as the age of the data used (both studies used UK data only up to 2005), meant that they did not feel sufficient confidence in the finding to retain age as a risk factor for multidrug resistance amongst people with tuberculosis. The group also noted that there was an increased odds of multidrug resistance in patients with smear positive disease, but the small size of the population and wide confidence intervals meant that they did not feel confident that this would be a useful component of the risk assessment. Evidence for 'residence in London' as a risk factor was obtained from an unmatched case-control that examined data that was not current. Additionally, the multivariate analysis only adjusted for age and for the period from which the data was derived (1993-4 and 1998-2000). Evidence was limited for 'a history of tuberculosis' as a risk factor, as this was often used to differentiate subgroups rather than as a risk factor itself. The group also noted that 'contact with a known case of multidrug resistant tuberculosis' might have been underestimated, as a high proportion may not know that they have been exposed.

5.2.73 Recommendations

88. For people with clinically suspected TB, a TB specialist should request rapid diagnostic nucleic acid amplification tests for rifampicin resistance on primary specimens if a risk assessment for multidrug resistance identifies any of the following risk factors:

- history of previous TB drug treatment, particularly if there was known to be poor adherence to that treatment
- contact with a known case of multidrug-resistant TB
- birth or residence in a country in which the World Health Organization reports that a high proportion (5% or more) of new TB cases are multidrug-resistant. **[new 2015]**

Update 2015

5.3 Identifying drug resistance

5.3.1 Clinical introduction

Multidrug-resistant (MDR) TB is defined as resistance to, at least, rifampicin and isoniazid - the two most powerful first-line anti-TB drugs. MDR-TB has a worse patient outcome than drug sensitive disease.

The conventional diagnostic work up for patients with suspected pulmonary TB disease includes sputum smear microscopy to provide an early indication of infectivity (see section 3.3), followed by culture to confirm diagnosis and for drug sensitivity testing (DST). Culture is considered the gold or reference standard, but takes up to 6 weeks for a definitive result. Rapid molecular assays can have a result in as little as 1 to 3 days. This more rapid diagnostic process can potentially be beneficial for patients, the community and the NHS.

However, rapid assays are less accurate than culture, raising the possibility of false positive and false negative results. Both types of error can be costly and harmful. These harms are likely to be particularly acute for patients with, or at high perceived risk of, MDR-TB. Current practice is that rapid molecular tests have a role alongside culture, but that they, at the moment, do not replace culture.

During the development of this guideline, an NIHR funded health technology assessment into the effectiveness and cost effectiveness of molecular genetic tests for drug resistance was undertaken (http://www.journalslibrary.nihr.ac.uk/hta/volume-19/issue-34). The investigators made prepublication results from their work available to the GDG; these were discussed at multiple GDG meetings and treated like any published material identified in a systematic review would be. The report comprised a systematic review of evidence regarding the diagnostic accuracy of molecular genetic tests for drug resistance, a health economic model comparing diagnostic tests and local versus regional laboratory testing policies, and a transmission-dynamic mathematical model evaluating the clinical impact of those strategies.

Update 2015

5.3.2 Review question

What is the diagnostic accuracy of molecular genetic tests for drug resistance.

5.3.3 Evidence review

A standardised search strategy (PROSPERO registration: CRD42011001537; Appendix 1), was designed to generate a comprehensive list of relevant studies from five electronic literature databases: EMBASE, PUBMED, MEDLINE, BIOSIS, Web of Science. The strategy design was based upon a previously successful model employed by ECDC. It was further validated by comparing the citation output against the bibliography of two published diagnostic reviews of rapid diagnostic tests for tuberculosis and drug susceptibility.

Additional sources were checked to ensure that the review included studies that were not missed. These included: CINAHL (Cumulative Index to Nursing and Allied Health Literature), NHS EED (NHS Economic Evaluation Database), SIGLE, diagnostic equipment manufacturer websites and experts within the field. Additional hand searching was carried out to identify papers using the citation lists of published diagnostic accuracy reviews 45,46. In addition, when study authors were

Studies were included in the review if they met the inclusion criteria listed below. Studies that met these criteria were included irrespective of the published language, the country of origin or their current publication status i.e. grey-literature, published or in press).

The eligibility criteria were as follows:

- Studies that assessed rapid genetic diagnostic methods to detect drug susceptibility of M. tuberculosis.
- Studies that used human clinical samples.
- Studies that compared the results of the rapid (index) test with sequencing or a culture based sequencing drug susceptibility test (DST) as a reference standard.
- Studies that reported sufficient data to calculate the true positive (TP), true negative (TN), false positive (FP) and false negative (FN) of the rapid diagnostic test.
- Studies that reported at least 10 samples susceptible to the drug of interest and 10 samples that were resistant to the drug of interest, identified by the reference standard.

A total of 8,922 titles and abstracts were identified through database searches and hand-searching. After the first phase of screening 557 papers were identified as potentially eligible for the review. A total of 57 studies contained sufficient information on the performance of the rapid diagnostic tests to be included in the review.

5.3.44 Health economic evidence

In 2015 an NIHR-funded report conducted a systematic review of evidence regarding the diagnostic accuracy of molecular genetic tests for drug resistance (http://www.journalslibrary.nihr.ac.uk/hta/volume-19/issue-34). The evidence from this review was used to parameterise a health economic model comparing diagnostic tests and local versus regional laboratory testing policies, whilst a transmission-dynamic mathematical model was developed to evaluate the clinical impact of those strategies. Although it was not due for publication during the development phase of this guideline update, the GDG was aware of this project, as several members were co-investigators. For this reason, the investigators made pre-publication results available for the GDG's consideration. This material was treated as any other publication would be according to guideline development methods; accordingly, it was critically appraised and summarised by the technical team and presented to the GDG as relevant evidence (see below).

In the model, the baseline for comparison was smear microscopy, culture for identification of MTB and drug susceptibility testing (DST) for culture-positive cases. The intervention evaluated was the addition of a rapid molecular assay for the detection of TB disease and drug resistance to the current diagnostic strategy. The interventions considered were the INNO-LiPA Rif.TB, GeneXpert MTB/RIF and GenoType MTBDRplus The analysis did not distinguish between different patterns of drug resistance, so that patients with mono-resistance (other than for rifampicin) do not incur significant additional risks or costs for isolation or drug treatment compared with patients with drug-sensitive disease. It was also assumed that patients with different patterns of multiple drug resistance face similar risks and costs as each other.

The analysis was conducted from a NHS/PSS perspective with costs and benefits discounted at 3.5% per annum. The model included a detailed breakdown of the costs of TB treatment, including admissions, outpatient appointments, TB specialist nurse time, and infection control measures covering inpatient isolation in wards, side rooms and negative-pressure facilities. These costs and those of standard diagnostic tests (Mantoux, IGRA, blood testing, smear, LFT and CXR) were taken from NHS Reference Costs. The costs of the rapid assays and culture testing (for MTB diagnosis and DST testing) both at regional and local laboratories, were based on local data from the UK Public Health England National Mycobacterium Reference Laboratory. Treatment costs for latent, active and drug-resistant tuberculosis were taken from the BNF. Data on the point of referral for TB diagnosis – GP referral, A&E attendance, and inpatient referrals – and associated resource (CXR and blood tests) use was derived from expert opinion.

Health-related quality of life was measured on a QALY scale. The baseline quality of life utility value was taken from the Health Survey for England, whilst utility losses due to active

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TB were taken from Kruijshaar et al who describe QALY decrements associated with pre-treatment active TB, and on-treatment TB in both inpatient and outpatient settings. Mean QALY losses due to TB mortality were calculated based on the transmission dynamic model. The model considered that patients undergoing treatment for MDR-TB had a 42% chance of experiencing permanent hearing loss as a result of treatment toxicity, although this probability was adjusted pro-rata for the duration of treatment. In the base case of the model, 4 months of therapy for MDR TB incurs harms amounting to 1.03 QALYs lost per person treated.

The analysis considered the implementation of rapid molecular tests for drug resistance in three populations: south Asians, black Africans and eastern Europeans. These groups were considered because they account for the majority of TB in England and Wales, with eastern Europeans having a disproportionate burden of MDR disease. The necessary epidemiological data to model transmission was only available for the first 2 of these groups, and the model assumes that transmission only occurs within, and not between, ethnic groups.

In the base case, the analysis suggests that all molecular testing strategies dominate (are both less costly and provide QALY gain compared with) strategies using smear, culture and DST alone in, south Asian, black African and eastern European populations. For south Asians, potential population-level health gains are estimated at approximately 300–900 QALYs, with potential cost savings of around £25M–£30M. For black Africans, potential population-level health impacts are estimated at between approximately 20 QALYs lost and 500 QALYs gained, with potential cost savings of around £20M–£23M. For eastern Europeans, potential population-level health gains are estimated at approximately 0–10 QALYs, with potential cost savings of a little over £1M.

A deterministic sensitivity analysis showed that model outputs varied with the diagnostic accuracy parameter inputs, but net monetary benefit remained positive in all cases except the use of MDTBRPlus for eastern Europeans, where the uncertainty around the test's ability to correctly detect TB meant that INB was negative at the lower limits of that parameter. It is unclear whether the ability to consider transmission dynamics in this population would alter this.

The PSA results support the base-case findings, although there is greater uncertainty as to whether rapid diagnostics should be employed at regional or local laboratory level. However, as no deterministic sensitivity analysis was undertaken for this comparison it is not possible to ascertain what parameter inputs are driving this uncertainty. It is noteworthy that many of the costs and resource-use assumptions for this comparison were based largely on expert opinion, and therefore the analysis may be a significant over- or underestimate of the true uncertainty present.

5.3.5 Evidence statements

GeneXpert

Low quality evidence from 6 studies reported sensitivity and specificity of the GeneXpert test varied between 81.3-100.0% and 97.4-100.0% respectively. The pooled estimates of sensitivity (96.8%,95% CI: 94.2-99.4%) and specificity (98.4%, 95% CI: 97.8-99.0) suggested a high level of diagnostic accuracy when this test was used to detect rifampicin resistance in clinical samples.

INNO-LiPA

Low quality evidence from 9 studies reported sensitivity and specificity of the INNO-LiPA test varied between 86.7-100.0% and 82.4-100.0% respectively). The pooled estimates of sensitivity (95.4%, 95% CI: 92.2-98.3%) and specificity (99.7%, 95% CI: 99.5-100.0)

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suggested a high level of diagnostic accuracy when this test was used to detect rifampicin resistance in clinical samples.

GenoType MTBDRplus

Low quality evidence from 19 studies reported sensitivity and specificity of the MTBDRplus to detect resistance to rifampicin ranged between 82.1-100.0% and 89.9-100.0% respectively. The pooled estimates of sensitivity (94.6%, 95% CI: 91.6-97.6%) and specificity (98.2%, 95% CI: 97.2-99.3) suggested a high level of diagnostic accuracy when this test was used to detect rifampicin resistance in clinical samples.

GenoType MTBDRsl

A total of 6 studies reporting the use of MTBDRsl met the inclusion criteria for the review. These studies reported the diagnostic accuracy of MTBDRsl to detect resistance to a range of detection of injectable drugs and fluroquinolones resistance in clinical samples. However, the sample size for each drug category of interest was limited, and only the groups of studies reporting diagnostic accuracy for specific dugs were not sufficiently large for meta-analysis.

Health economics

One directly applicable study with potentially serious limitations examined the cost effectiveness of adding a rapid diagnostic test to standard smear, culture and DST testing in South Asian, Black African, and Eastern European populations. The analysis suggested that the addition of rapid molecular testing to standard practice was the dominant strategy. Significant uncertainty was present in the structural and parameter aspects of the modelling used, and the results may not be generally applicable to TB patients outside the groups considered.

5.3.6 Evidence to recommendations

Relative value of different outcomes	The GDG noted that, in practice, there is a trade-off between sensitivity and specificity for many tests. Although the GDG would prefer to recommend tests that perform well on both measures, on discussing their relative importance the group felt that sensitivity, and the capacity of highly sensitive tests to rule out disease, was more important to their decision-making. The prognostic value of tests was also considered important for decision-making, as were the acceptability of approach to the patient or clinician and the incidence of adverse events associated with different diagnostic approaches, though these outcomes were not considered critical. Despite this, no data on these outcomes was identified in the included papers.
Trade off between clincial benefits and harms	People incorrectly considered to have MDR-TB may benefit from an early rule-out: avoiding or shortening unnecessary isolation and treatment with its associated high costs (for the patient as drug-related adverse events, and the health service in terms of hospital admission and negative pressure isolation). For patients with disease, early accurate diagnosis will ensure that they commence effective treatment promptly and that where necessary they are isolated earlier. False negative results provide inappropriate reassurance, and may harm the patient by delaying time to effective treatment and placing contacts at risk of infection control measures are relaxed. False positive results may unnecessarily expose patients to the inconvenience of isolation and adverse effects of medication. Although the data for rapid drug susceptibility tests was broken down by the specific test used, the group felt it was important that any guidance issued on the use of such tests should not be over-prescriptive with regard to the specific test or type of test that should be used. This is because the field of

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	rapid diagnostics is fast-moving, and may have moved on before this guidance is reviewed.
Trade-off between net health benefits and resource use	The GDG reviewed the evidence for the use of rapid molecular tests in South Asian, Black African and Eastern European populations. The GDG felt that a lack of model transparency meant that the results should be interpreted with caution. The GDG noted that in addition to the sensitivity analysis presented, the model was based on treatment assumptions which may not represent the full range of current clinical practice with regard to the presumptive treatment of a patient with a (clinically perceived) high risk of MDR-TB whilst waiting for culture based DST confirmation. In the model, patients who are incorrectly suspected of having MDR-TB are started on treatment and therefore potentially unnecessarily exposed to MDR drugs which are toxic and carry (in this analysis) a significant associated utility decrement, although this parameter is fixed in the model and not explored in any sensitivity analysis. These patients, and true-positive patients, will also be isolated in expensive negative pressure isolation. The GDG discussed that there is likely to be a QALY loss which is related to the duration of isolation, which is not included in the analysis and therefore only the cost consequences of reducing unescesary isolation could be considered. There are also benefits to patients who are correctly diagnosed earlier than would occur using traditional smear, culture and DST methods, including patients who would be classed as smear negative (but who may be MDR+ve) . These true-positive patients are treated sooner, with the correct regimen, and therefore experience reduced time wth TB related morbidity. Isolating these patients reduces the onward transmission of MDR TB, although the GDG noted that the model shows that transmission levels within the groups described are low, and that the overall impact of rapid diagnostic methods on TB transmission is also minimal. The GDG discussed the whole population approach taken to the evaluation of rapid diagnostics within the 3 groups. It commented that it would have liked to have seen an analysis that explicitly considered the cost effectiveness of a targeted approach – that is reserving the use of rapid diagnostics for those cases where the relative risk of MDR or drug-resistant TB is deemed to be elevated. The GDG considered that this approach could be expected to have most of the benefits of the universal approach and few of the harms. The univariate sensitivity analysis undertaken by the investigators suggested that the cost effectiveness of the tests is sensitive to the prevalence of drug-resistant TB in the tested population. The GDG inferred that, in a subgroup of patients at high risk of drug-resistant TB, the tests would have higher positive predictive value (owing to higher prevalence of drug-resistant TB), and this would maximise the benefits of testing. Conversely the potential harms should also be minimised by adopting a targeted approach: the tests are not 100% specific, but there would be proportionally lower false-positives in high-risk patients and proportionally more in the low-risk group. Therefore, a blanket approach would be likely to result in more false positives, whereas they would be minimised therefore under a targeted approach. According to this rationale, the GDG inferred that a targeted approach would be certain to be cost-effective compared with DST alone, and very likely to provide similar or better value than the universal approach. It would also be associated with lower absolute costs (due to fewer tests performed). The GDG also felt that it would be difficult to justify a recommendation for universal molecular testing on the basis of modelling that was subject to acknowledged structural uncertainty and (only partially explored) parameter uncertainty. For these reasons, the GDG chose to recommend that the use of rapid diagnostic techniques should be targeted at people who have the highest risk of drug-resistant TB (see section 5.2). The GDG also formulated a

	research recommendation for the assessment of the clinical and cost-effectiveness of the targeted strategy.
Quality of evidence	The GDG agreed that the quality of evidence was low. There were concerns of possible biases introduced by the samples used, and there was often a marked lack of clarity surrounding the timing of the index and reference tests, the thresholds used for test interpretation and the reasons for exclusion. There were also issues identified with the quality of methodological reporting with studies using MTBDRplus. The lack of detail regarding timing, thresholds, patient selection and blinding resulted in the majority of studies classified as either high bias or unclear bias in the four key QUADAS domains. The authors identify the lack of sub-category analyses to explore heterogeneity as a key limitation of this work. This heterogeneity may be statistical heterogeneity, for example caused by methodological differences or clinical heterogeneity, and the authors noted that there was often insufficient methodological and recruitment detail reported to systematically record these differences, as few studies reported in detail on issues such as blinding or study design. The GDG agreed that the findings should be interpreted with caution due to high levels of heterogeneity level of heterogeneity across the evidence base.
Other considerations	None.

5.3.72 Recommendations

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89. If the rapid diagnostic nucleic acid amplification test for rifampicin resistance is positive:

- start infection control measures and continue until pulmonary disease has been excluded
- manage treatment along with a multidisciplinary team with experience of managing multidrug-resistant TB
- offer a treatment regimen involving at least 6 drugs to which the mycobacterium is likely to be sensitive
- test for resistance to second-line drugs. **[new 2015]**

90. If the rapid diagnostic nucleic acid amplification test for the *M. tuberculosis* complex is positive but rifampicin resistance is not detected, treat as drug-susceptible TB with the standard regimen. [new 2015]

91. If the rapid diagnostic nucleic acid amplification test for the *M. tuberculosis* complex is negative in a person at high risk of multidrug-resistant TB:

- obtain further specimens for nucleic acid amplification testing and culture, if possible
- use rapid rifampicin resistance detection on cultures that become positive for the *M. tuberculosis* complex
- consider waiting for the results of further tests before starting treatment if the person is well
- if urgent treatment is necessary, consider managing as multidrug-resistant TB until sensitivity results are available. **[new 2015]**

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92. When definitive phenotypic susceptibility results are available, modify treatment as needed. [new 2015]

93. Consider more intensive clinical follow-up for people with multidrug-resistant TB. This includes those having directly observed therapy throughout treatment because of the complexity of treatment and risk of adverse events. [new 2015]

5.4 Referral

5.4.1 Clinical introduction

MDR TB comprises some 0.8–0.9% of culture-confirmed TB cases in the UK, mainly in England and Wales.{140} As such they represent only 30–40 cases per year in number, but they have disproportionate importance because of:

- a prolonged infectious potential in pulmonary disease
- the need for higher levels of infection control, with negative pressure ventilated side wards, because of this and the potential adverse effects of acquiring the organism
- a much greater cost to treat, a minimum of £50–70,000 per case{211}
- prolonged treatment, often requiring multiple second-line drugs with an increased toxicity profile
- worse cure and survival rates, in both HIV-negative and HIV-positive individuals{226–230}
- the risk to healthcare workers and other contacts if they become infected.

Because treatment is complex, time consuming and demanding on both the patient and the physician, practice to date, based on BTS guidelines for treatment,{68} has been that treatment is only carried out:

- by physicians with substantial experience in drug-resistant TB
- in hospitals with appropriate isolation facilities (a negative pressure room)
- in close conjunction with the HPA and HPA regional centres for mycobacteriology.

Drug treatment of these cases is not addressed by this guideline, as it is a rare, highly specialised and highly individualised activity, which may include second-line drugs, close monitoring, full supervision of treatment and surgical options. It is therefore the concern of this guideline to promote transfer of patients to an appropriate unit.

5.4.2 Methodological introduction

A retrospective cohort study{231} performed in the USA was identified, which examined the treatment experience of patients diagnosed with MDR TB who were managed for at least part of their time on treatment in a specialist TB hospital. This study was excluded due to limitations in the methodology.

No studies of sufficient quality were found pertaining to whom (or where) MDR TB patients should be referred in order for them to achieve the most favourable treatment outcomes. Therefore, no evidence statements have been made in this section.

5.4.3 From evidence to recommendations

The GDG were aware that there are still relatively few cases of MDR TB in the UK each year, but noted that this represents a vitally important area in TB control and a unique challenge for treatment. The GDG felt that treatment failure (non-concordance) is a significant risk factor for drug resistance.

People with MDR TB are not always treated under the care of an MDR TB specialist. It was felt that there had been no evidence to support change in current practice in MDR TB referral since the BTS's code of practice.{6}

Patient acceptability and shared care arrangements need to be considered when arranging referral, and hence this section gives recommendations for discussing and consulting with specialist colleagues.

5.4.47 Recommendations

94. Discuss the options for organising care for people with multidrug-resistant TB with clinicians who specialise in this. Seek the patient's views and take them into account, and consider shared care. [2006]

5.5 Drug treatment for drug-resistant tuberculosis (excluding multidrug- and extensively drug-resistant tuberculosis)

5.5.1 Clinical introduction

Given the complexity of management in patients with drug-resistant tuberculosis, treatment decisions should be carried out in conjunction with specialist physicians with appropriate experience in managing such cases. Guidance for the drug treatment of patients with drug-resistant tuberculosis, excluding multidrug- and extensively drug-resistant tuberculosis, is set out below. In the case of multidrug- and extensively drug-resistant tuberculosis, however, management should *only* be carried specialist physicians with appropriate experience in managing such cases, on a case-by-case basis. As stated above, treatment of these rare cases is a highly specialised and highly individualised activity, which may include second-line drugs, close monitoring, full supervision of treatment and surgical options. These patients should therefore be referred to an appropriate unit.

5.5.2 Review questions

In people with drug-resistant tuberculosis (excluding MDR- and XDR-v tuberculosis) what is the most effective regimen of anti-tuberculosis drugs for reducing mortality and morbidity?

In people with drug-resistant tuberculosis (excluding MDR- and XDR-v tuberculosis) receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity?

In people with drug-resistant tuberculosis (excluding MDR- and XDR-v tuberculosis) are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?

5.5.3 Evidence review

For these review questions, one search strategy was developed and search undertaken. Papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy to pull in all papers relating to the administration of chemotherapeutic treatment for active tuberculosis in children. Only controlled trials were considered for inclusion.

Papers of interest were those that compared one treatment programme against other programmes with differing drugs or combinations of drugs, durations of treatment or daily/intermittent dosing regimens, in those with drug-resistant active tuberculosis at any site of the body. These papers had to include follow-up for at least the full time period of treatment. Where a study had been published at differing points during the follow-up period data from the paper with the longest follow-up time was extracted.

There were papers identified that included a mixture of treatment groups, usually both those with drug susceptible and those with drug-resistant tuberculosis. These papers were included if the data for the drug-resistant group had been reported separately, if this had not occurred the papers were excluded.

Papers were excluded if they were in those with MDR- or XDR- tuberculosis or had drug susceptible or latent tuberculosis. Those comparing drug regimens that included drugs not licensed in the UK were also excluded.

There were 1408 titles/abstracts hits from the search, of these 67 full-text papers were ordered. A further two papers were identified from a review paper by GDG members. Of

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these 17 met the inclusion criteria. Two included participants who all had drug-resistant tuberculosis. The remaining studies included participants who were drug-susceptible and those who were drug-resistant and had reported outcomes for both groups (Balasubramanian et al, 1990; East and Central African/ British MRC, 1983; East African/ British MRC, 1977; Hong Kong Chest Service/ British MRC, 1977; Hong Kong Chest Service/British MRC, 1979; Hong Kong Chest Service/British MRC, 1987; Tuberculosis Research Centre, Madras and National Tuberculosis Institute, Bangalore, 1986; Tanzania/British MRC Collaboration Investigation, 1996; Kleeberg, 1987; Tuberculosis Research Centre/Indian Council of Medical Research, Chennai, 1997; Santha et al, 1989; Singapore Tuberculosis Service/British MRC, 1988; Singapore Tuberculosis Service/British MRC, 1981; Tanzania/British Medical Research Council, 1985; Tuberculosis Research Centre, 1983).

The evidence from the included studies, relating specifically to bacteriological response in those with isoniazid resistance, is summarised in the table below. Full evidence tables are available in Appendix D.

5.5.4 Health economic evidence

An economic evaluations filter was applied to the search protocol and 730 records were returned. After a title and abstract sift, no records were found that matched the inclusion criteria.

5.5.5 Evidence statements

Very low quality evidence from a single randomised controlled trial found less than 7RE (for an explanation of the abbreviation system for treatment strategies, see section 13.2) to be associated with higher rates of response than 4RE but there were no significant difference between the groups for either adverse effects or relapse rates in people with drug-resistant tuberculosis.

3RSZH or 3RSHZ + 2SHZ

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 91% and a relapse rate at 19% at 5 years

6RSH

Very low quality evidence from 2 randomised controlled trials of mixed drug-resistant / drug-susceptible patients reported response rates of 85% and 95% and relapse rates of 14% and 23% at between 24 and 30 months.

SHRZ/$S_2H_2Z_2$

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 80% and a relapse rate at 21% at 2 years

SHRE/$S_2H_2Z_2$ SHR

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 100% and a relapse rate at 43% at 2 years

$S_3H_3Z_3R_3/S_2H_2Z_2$

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 95% and a relapse rate at 13% at 2 years

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3RSZH

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 94% and a relapse rate at 21% at 2 years

6SRZH

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 67% and a relapse rate at 20% over an unspecified timeframe.

$2EHRZ_2/4EHR_2$

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 80% and a relapse rate at 54% over an unspecified timeframe.

$2EHRZ_7/6EH_7$

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 83% and a relapse rate at 29% over an unspecified timeframe.

$2HRZ_2/4HR_2$

Very low quality evidence from a single randomised controlled trial of mixed drug-resistant / drug-susceptible patients reported a response rate of 38% and a relapse rate at 19% over an unspecified timeframe.

5.5.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the treatment approaches used within the included studies and noted that the papers did not use combinations of drugs that reflects what would be in use in the UK. The group noted and discussed that the importance of appropriately treating those with tuberculosis that is resistant to a single drug, specifically within the UK in relation to isoniazid resistance. The group noted that there may be inconsistencies in the treatment offered in current practice and discussed the importance both to the individual and the public health implications of ensuring that drug-resistant tuberculosis is appropriately treated.
Trade-off between benefits and harms	The GDG discussed the significance of the appropriate treatment for drug-resistant tuberculosis, both for the individual patient and in a public health context. The majority of the available evidence involved considerably varying regimens in terms of both drugs and doses used and duration of treatment. The heterogeneity of this data made distilling out differences between regimens and ascertaining those which provided more benefit to patients very difficult. Nonetheless the GDG considered that there was some weak evidence for treatment length of longer than 6months. The group further discussed the characteristics of the drugs in the regimens where isoniazid cannot be included due to resistance. Though the group also expressed concerns regarding treatment periods that may be unnecessarily long and the impact that they have on the patient. They agreed that the continuation phase should be 7 months (this should only be extended where there are specific adherence concerns or where disease is extensive). Although the evidence is limited and using the GRADE analysis the evidence all rated as very low. The group considered that the evidence does not demonstrate the safety of intermittent regimens and that the daily treatment recommendations should be retained. The group agreed that drugs and regimens within the current

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	recommendations, in light of the evidence presented and their expert opinion should be retained. The group noted that no evidence had been found in relation to CNS drug-resistant tuberculosis. They considered that with no evidence in this area and the small numbers of patients presenting with it that the most suitable recommendation would be to ensure that these patients are referred to a specialist. The group considered that there was insufficient evidence for drug-resistance to other drugs than isoniazid. They noted that the recommendation for streptomycin resistance could be removed as streptomycin is not part of standard practice. Furthermore, given that rifampicin resistance is now a generally accepted proxy for multidrug resistance, treatment should be as for rifampicin resistance should be as for multidrug resistance (that is, by specialist physicians with appropriate experience in managing such cases). Otherwise, the group agreed that the current recommendations for these patients should be retained. The GDG agreed that there is a need for much clearer evidence in this area, in particular regarding the length of treatment required. They agreed to develop a research recommendation relating to the need for trials of 6month compared with 9month treatment regimens.
Trade-off between net health benefits and resource use	None identified.
Quality of evidence	The GDG did highlight that though this evidence viewed through the current quality processes is rated as very low quality, the evidence in these trials were among the first RCTs to be systematically conceived and completed. Nonetheless overall the quality of the evidence presented was low. With these limitations in the quality of the evidence, alongside the approaches being used not reflecting combinations of drugs that would be considered in current practice, the GDG viewed that their expert consensus and experience would be a substantive part of the evidence base for the development of the recommendations
Other considerations	None.

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5.5.7 Recommendations

95. For people with TB, without central nervous system involvement, that is resistant to just 1 drug consider the treatments in table 20.

Table 20: Recommended drug regimens for non-MDR drug-resistant TB

Drug resistance	First 2 months (initial phase)	Continue with (continuation phase)
Isoniazid	Rifampicin, pyrazinamide and ethambutol	Rifampicin and ethambutol for 7 months (up to 10 months for extensive disease)
Pyrazinamide	Rifampicin, isoniazid and ethambutol	Rifampicin and isoniazid for 7 months
Ethambutol	Rifampicin, isoniazid and pyrazinamide	Rifampicin and isoniazid for 4 months
Rifampicin	As for multidrug-resistant TB	

96. For people with drug-resistant TB and central nervous system involvement, involve a TB specialist with experience in managing drug-resistant TB in decisions about the most appropriate regimen and the duration of treatment. [new 2015]

5.5.8 Research recommendations

11. For isoniazid-resistant TB, what is the most effective regimen for reducing mortality and morbidity?

Why this is important

There is little evidence for the treatment of isoniazid resistant TB. This is the most common form of drug resistance in the UK, occurring in 7.5% of TB cases. Currently, treatment isn't always successful, even when the recommended drugs are given for the recommended time and there are no adherence issues. It is particularly difficult to treat if there are treatment interruptions or if the central nervous system is involved. Randomised controlled trials are needed to compare different anti-TB regimens for isoniazid-resistant TB, assessing mortality, treatment success or treatment failure, rates of relapse and adverse events.

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6 Infection control

6.1 Infection control measures

6.1.1 Clinical introduction

Infection control often encompasses a combination of measures aimed at minimizing the risk of TB transmission within population. Non-healthcare settings may include correctional facilities, military bases, homeless shelters, nursing homes, schools, etc. in which the length of stay of individuals may differ therefore, affecting the dynamics of TB transmission.

Even though congregate settings may adhere to different policies and differences in their approaches may be evident, in general, the same infection control principles applied to a national level in healthcare settings should also apply to non healthcare setting. Infection control in both healthcare and non healthcare settings may involve administrative, environmental, or personal protective controls.

6.1.2 Review question

For people in hospital who have active TB, what infection control measures are the most effective in preventing transmission of TB infection to others?

For people who have active TB who are not in hospital but who are in congregate settings (for example residential homes or homeless shelters), what infection control measures are the most effective in preventing transmission of TB infection to others?

6.1.3 Evidence review

This review focuses on TB transmission in healthcare (i.e. hospital) or non-healthcare settings.

Studies were included if they:

- included people exposed to TB in congregate settings
- examined the effectiveness of infection control measures in preventing TB transmission in healthcare and non healthcare congregate settings, including:
  - administrative: isolation or reduction in patients movements, reduced time to diagnosis/initiation of treatment, sample collections in isolation rooms, dedicated infection control staff, restricting/screening of visitors
  - engineering: isolation rooms (including negative pressure isolation rooms, sputum induction booths), droplet shields, improved ventilation (including extraction fans, laminar airflow), UV light
  - personal: patient mask-wearing, cough hygiene/behaviour
- measured the following outcomes
  - risk of tuberculosis infection or disease: number of cases of TB identified/number of people at risk or tested
  - acceptability of approach
  - risk of exposure: amount of contact with a case of TB
  - resource use and cost
  - health related quality of life

Full text randomized control trials, quasi-randomized control trials, non-randomized controlled trials and systematic reviews of these study types were selected; prospective

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observational studies were considered as insufficient evidence was found. Only studies in English were considered for inclusion.

Studies were excluded if they were:

- case series, case studies, descriptions of nosocomial outbreaks, narrative reviews and modelling studies
- studies that utilised questionnaire responses to ascertain prevalence or incidence of latent or active TB
- focused on air travel

A comprehensive search of electronic databases including CDSR, DARE, HTA database, CENTRAL, Medline, Medline in-process, EMBASE was conducted by an information specialist. The full search was conducted in two phases. The original search resulted in 6508 citations. 6391 records were excluded on citation screening, and 82 on abstract screening. 35 records were requested. On further examination at full text level, 33 records that did not meet the selection criteria were excluded. The World Health Organization (WHO)'s guideline for infection control in congregate settings[gg] was reviewed, as suggested by the GDG. While cross referencing citations it was noted that a number of search filters had prevented the retrieval pf important studies found in the WHO guideline. The search was then conducted again without filters, this time yielding 6664 records. In total, after citation, abstract and full text screening, 9 full text articles met the inclusion criteria.

Given the paucity of research in the area and the difficulties and ethical considerations needed for conducting an intervention of this kind, the GDG felt that any studies providing data on the population and outcomes of interest that would add evidence to support the recommendations on infection control should be considered for inclusion, regardless of design. The protocol was modified as needed.

6.1.4 Health economic evidence

A single literature review was undertaken for this question and the related one of duration of isolation (see section 6.2). An economic evaluations filter was applied to the search protocol for these questions with the aim of finding economic evaluations that explored the relative benefits, harms and costs of different methods of infection control and different durations of isolation. The search identified 2177 references. The references were screened on their titles and abstracts and none of the studies met the inclusion criteria.

6.1.5 Evidence statements

Very low quality evidence from 9 studies suggests that infectious control measures (administrative, environmental and personal) are effective in preventing transmission of TB infection to others in healthcare and non healthcare settings. Few adverse effects were reported. However, overall there was low confidence in the results.

3 studies implemented a combination of infectious control measures from the three levels mentioned above in a healthcare setting simultaneously. It is likely, as the literature points out, that infectious control measures need to be used as a package, and that few would be effective if implemented in isolation.

1 study explored participants' knowledge, as well as the acceptability of different infection control measures to patients.

4 studies explored ventilation three in nonhealthcare settings and 1 in a hospital setting. 2 studies found that ventilation rates were lower in households of individuals with TB infection.

[gg] World Health Organization (2009) WHO policy on TB infection control in health-care facilities, congregate settings and households. World Health Organization: Geneva

1 study was inconclusive about the effectiveness of ultraviolet germicidal irradiation for reducing the incidence of TST conversion (an indicator for TB transmission); however, the study found the incidence of adverse events for this type of measure to be ***.

6.1.64 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that the risk of tuberculosis infection or disease (for example, measured by the number of cases of TB identified against the number of people at risk or tested), the acceptability of approach to those they affect and the risk of exposure (that is, the impact of the intervention on the amount of contact with an infectious patient) were critical for decision making.
Trade-off between benefits and harms	The GDG recognised the importance of infectious control implementation for the reduction of TB transmission and the harms associated with the lack of implemented measures. Basic intervention measures like prompt identification of symptoms, isolation of infectious patients, use of masks, increased ventilation and negative pressure rooms when available were felt to provide benefits in healthcare settings and non healthcare settings alike. The GDG also recognised that efforts to overcome the difficulties in identifying individuals that are infectious but not symptomatic who present to hospitals or nonhealthcare settings should be made. They agreed that it is important to consider the impact of factors such as the age and HIV status of patients or those around them, as well as the drug susceptibility of the disease, which may affect the infectiousness of patients and the vulnerability of those around them. Such considerations may impact the decision to ask patients to wait in a separate waiting room or use a fasttrack queue system, for example. The group noted that patients with sputum smear-positive drug resistant disease are no more infectious than similar patients with fully susceptible disease; that is, they should not infect a higher proportion of contacts, because the organism is no more virulent. The consequences of acquiring multidrug resistant TB infection and then disease, however, are much more serious than for fully susceptible TB, because multidrug resistant TB needs prolonged treatment (often with more toxic second-line drugs) and the outcome in terms of death and proportions cured are worse. Because of the loss of the most effective killing drug (isoniazid), and the most effective sterilising drug (rifampicin), such patients take much longer to become noninfectious than if organisms are fully susceptible. In these cases there is not the rapid fall in numbers of viable organisms in the sputum seen in drug-susceptible cases, so they have a much prolonged infective potential after starting treatment. For these reasons, it has been advised that patients with suspected or proven multidrug-resistant TB should be isolated in a negative pressure room, and staff should wear FFP3 masks during patient contact whilst the patient is considered infectious. In addition, although the isolation of individuals believed to have infectious multidrug-resistant TB is a critical measure to prevent transmission, the GDG recognised that there are adverse effects associated with isolation, particularly in healthcare settings. These include boredom, a lack of contact with staff (and therefore potential for lower quality health care), poorer adherence to treatment, wandering around into other areas, potentially into areas with more vulnerable patients (such as the transplant ward). For these potential adverse effects of isolation, actions to counteract their potential harm to both the patient and those around them should be considered.
Trade-off between net health benefits and resource use	The GDG prioritised this review question, along with section 6.2 of the guideline, for original health economic analysis and considered the outputs of that work in making these recommendations. The GDG was interested in all aspects of this review question, but felt that the biggest areas of uncertainty from a health-economic perspective centred on inpatient isolation practice, and consequently asked that the de novo analysis

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	focussed on that area. The GDG considered the results of that work when making these recommendations, in addition to those in section 6.2.
Quality of evidence	The evidence from this review is derived from observational prospective interventional studies, a nested case control and a controlled field trial. Therefore, the match between the question, design/methods, subjects, measurements of outcomes, and protection against biases were judged to be suboptimal. On the other hand, the GDG was aware that the designs sought (e.g. RCT, quasi RCT) might not be possible as they pose an ethical dilemma difficult to solve. This, in part, may explain why most of studies found correspond to a lower hierarchical category of evidence. The GDG discussed the findings and noted the evidence ranged from low to very low, which implies the confidence in the effect estimate is very limited and the true effect is likely to be substantially different from the estimated effect. Also, while reviewing the engineered control measures the unit of analysis were environmental units.
Other considerations	The group noted the evidence was from countries in which the context, population under investigation and the health systems are known to differ greatly from the UK context. This was deemed important in considering the evidence. The GDG agreed that given the paucity of research in the area of infection control in healthcare and non healthcare settings the recommendations will include the evidence presented and consensus from the group.

6.1.71 Recommendations

These recommendations deal with 3 levels of isolation for infection control in hospital settings:

- negative-pressure rooms, which have air pressure continuously or automatically measured, as defined by NHS Estates
- single rooms that are not negative pressure but are vented to the outside of the building
- beds on a ward, where standard ventilation is in place.

Healthcare settings

97. Ensure healthcare settings can promptly identify people with suspected infectious or confirmed pulmonary TB before or at presentation. Ensure people working in the settings follow the recommendations about testing and treatments. [new 2015]

98. Put patients with suspected infectious or confirmed pulmonary TB who will remain in a hospital setting (including emergency, outpatients or inpatient care) in a single room. If this is not possible, keep the person's waiting times to a minimum. This may involve prioritising their care above that of other patients. [new 2015]

99. Minimise the number and duration of visits a person with TB makes to an outpatient department while they are still infectious. To minimise the risk of infection, people with infectious TB should be seen at times or in places away from other patients. [new 2015]

100. In hospital settings, risk assess people with suspected infectious or confirmed pulmonary TB for multidrug-resistant TB. Care for those deemed to be at low risk in a single room, as a minimum. For those deemed to be at high risk:

- provide care in a negative pressure room, and

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- have specimens sent for rapid diagnostic tests, such as nucleic acid amplification tests. **[new 2015]**

101. Unless there is a clear clinical or public health need, such as homelessness, people with suspected infectious or confirmed pulmonary TB should not be admitted to hospital for diagnostic tests or for care. [2006, amended 2015]

102. Do not admit people with suspected infectious or confirmed pulmonary TB to a ward containing immunocompromised patients, such as transplant recipients, people with HIV and those on anti-tumour necrosis factor alpha or other biologics, unless they can be cared for in a negative-pressure room on the same ward. [new 2015]

103. Assess any visitors to a child with suspected active TB in hospital for symptoms of infectious TB, and keep them separate from other patients until they have been excluded as a source of infection. [new 2015]

104. In people who may have TB, only carry out aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment in an appropriately engineered and ventilated area (ideally a negative pressure room). [new 2015]

105. Ask inpatients with suspected infectious or confirmed pulmonary TB (with explanation) to wear a surgical mask in the hospital whenever they leave their room, until they have had at least 2 weeks of treatment. [2015]

106. Offer patients advice on simple respiratory hygiene measures. [new 2015]

Non-healthcare settings

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107. In non-healthcare settings catering for large numbers of people and populations at high risk of TB (such as detention settings, residential hostels and day centres):

- promote simple respiratory hygiene
- ensure awareness of symptoms of potentially infectious TB to enable prompt healthcare referral
- seek advice from the local public health team and the local authority on accommodating people with TB
- ensure adequate ventilation. **[new 2015]**

Multidrug-resistant TB

108. If people with suspected or known infectious multidrug-resistant TB are admitted to hospital, admit them to a negative-pressure room. If none is available locally, transfer them to a hospital that has these facilities and a clinician experienced in managing complex drug-resistant cases. Carry out care in a negative-pressure room for people with:

- suspected multidrug-resistant TB, until non-resistance is confirmed
- confirmed multidrug-resistant TB, until they have 3 negative smears at weekly intervals and are ideally culture negative. **[new 2015]**

109. For people with confirmed multidrug-resistant TB whose symptoms have improved and who are unable to produce sputum, discharge decisions should be taken by the multidisciplinary team and the health protection team. [new 2015]

110. Staff and visitors should wear FFP3 masks during contact with a patient with suspected or known multidrug-resistant TB while the patient is thought to be infectious. [2015]

111. Before deciding to discharge a patient with suspected or known multidrug-resistant TB from hospital, agree with the patient and carers secure arrangements for supervising and administering all anti-TB therapy. [2015]

112. Discuss the decision to discharge a patient with suspected or known multidrug-resistant TB with:

- the infection control team
- the local microbiologist
- the local TB service and
- the health protection team. **[2015]**

113. Ensure negative-pressure rooms used for infection control in multidrug-resistant TB meet the standards of the Interdepartmental Working Group on Tuberculosis, and are clearly identified for staff, for example by a standard sign. Keep such signs up to date. [2015]

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6.2 Duration of isolation

6.2.1 Clinical introduction

It is known that individuals who are sputum microscopy positive from spontaneously expectorated sputum are those cases with the highest infectivity, and pose a risk of infection to others. There is consensus on the need for these individuals in whom active tuberculosis is suspected to be placed in airborne isolation; however the duration of infectiousness and the consequent period of isolation required remain unclear.

If individuals are sputum microscopy positive, and admitted to hospital, isolation is required until drug therapy makes the individual non-infectious. Isolation has been recommended until three separate and consecutive sputum tests have been analysed and present negative results (i.e. negative concentration of bacilli). If these consecutive sputum tests are negative, the patient is usually deemed to pose a significantly lower infection risk and can be removed from isolation over at least a 2-day period (in addition to a clinical assessment). The initiation of drug therapy causes a rapid fall in viable organisms in the sputum, even if acid fast bacilli (AFB) are still visible on microscopy, infectivity decreases.

This review focused on the length of isolation needed for people with active tuberculosis (TB), to minimise the risk of infection. As well, this review investigated what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation

6.2.2 Review questions

For people who have active TB what duration of isolation is necessary to minimise the risk of infection to others? And what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation?

For people who have active TB that is not suspected to be MDR-TB, what duration of isolation is necessary to minimise the risk of infection to others. For people who have active TB that is suspected to be MDR-TB, what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation?

6.2.35 Evidence review

A comprehensive search of electronic databases including CDSR, DARE, HTA database, CENTRAL, Medline, Medline in-process, EMBASE was conducted by an information service specialist from database inception to December 2014. We applied language restrictions. The search strategy for each database is presented in Appendix A.

Studies were included if they

- included people who have active TB;
- measured:
  - isolation periods of varying duration, or
  - clinical signs, symptoms or measurements that indicate whether a person with active TB poses a continued risk of infection to others;
- reported:
  - risk of TB infection or disease;
  - risk of exposure: amount of contact with a case of TB;
  - acceptability of approach (adverse effects);
  - relationship between clinical factors and risk of diagnosis (microbiological) of active or latent TB in another person;
  - resource use and cost;
  - health-related quality of life.

Studies were excluded if they were were case series, case studies, descriptions of nosocomial outbreaks, narrative reviews or modelling studies.

The search resulted in 7859 citations. 6775 were excluded on citation screening and 1060 on abstract screening. 24 full papers were requested. On examination of full text articles, 16 records that did not meet the selection criteria were excluded. 8 articles were included.

6.2.49 Health economic evidence

The systematic literature review for this question was combined with that for different methods of infection control. No relevant cost–utility analyses were identified.

The GDG prioritised this review question for original health economic analysis because they felt that this was an area of clinical care with significant costs and quality of life dimensions that were poorly described in the current evidence base. Isolation beds are more expensive than regular inpatient beds, and few studies have considered the quality of life implications of inpatient isolation (none with specific reference to TB). The clinical effectiveness of such infection control practices has been largely inferred from studies of TB outbreaks and animal infection. Therefore, the GDG was keen to explore the benefits, harms and costs of isolating patients with infectious TB, taking into account the environment into which the patient would be discharged, if patients were not judged to be at need of isolation.

The starting point for this analysis was the existing recommendation that patients with suspected infectious TB, who are deemed to be at low risk of drug resistance, should be isolated in a side-room and given appropriate drug therapy. Assuming that treatment is adhered to, and clinical improvement occurs, patients with drug susceptible disease may be released from isolation after 14 days. The model assumes that this duration of isolation and

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therapy is 100% effective at preventing onward transmission of TB. It then considers the comparative costs, benefits and harms of reducing isolation to 7 days.

Different approaches were used to simulate people being discharged to their usual place of residence and those who would be cared for on an inpatient ward if isolation were discontinued. For discharge to the community, the analysis used a simple mathematical model, parameterised from a Dutch contact-tracing study (Lohmann et al. 2012), which details the statistical relationships between duration of TB, initial smear grade and contact setting. Because the relative proportion of subsequent latent and active TB cases caused by each index case can be derived from this study, the relative infectiousness of index cases can be used to calculate the expected number of infections caused given smear grade, setting and duration of TB in the original model. The base case used a simple assumption of constant infectiousness over the period of interest; scenario analyses explored the impact of increasing and decreasing infectiousness. Separate results were generated for people being discharged to home and those being discharged to a congregate setting (Lohmann et al. provide a proxy for this by detailing attendance or employment at a school as a determinnat of disease transmission).

In the case of a patient being discharged from isolation onto a ward, a separate mathematical model of airborne dispersal was used to calculate the probability of transmission. An review of potential models was undertaken, and the approach described by Gammaitoni and Nucci (1997) was selected based on published application to TB infection modelling. A full description of the equations and parameters used in this model is outlined in Appendix F. The relative expectation of proportions of LTBI and active TB infections caused according to index smear grade was estimated using the same evidence that was used when simulating people being discharged to the community (Lohmann et al. 2012). This was applied to the infections predicted by the dispersal model, and subsequent cost and QALY impacts were calculated.

For both analyses, it was necessary to estimate the long-term harms and costs associated with the secondary cases of TB that might occur if potentially infectious people were discharged from isolation. For cases of active TB, a fixed average cost of treatment was applied, and QALY losses were calculated that took account of disease- and treatment-related morbidity as well as the probability of acute TB-related death. For latent TB infection, a submodel was used to estimate the discounted costs and QALYs associated with each case. This was a Markov model with a 3-month cycle length, and a lifetime time horizon.

In the base-case analysis, isolating patients for 2 weeks before discharging them to the community results in comparatively little reduction in QALY losses compared with shorter isolation (7 days), but does increase costs (see table 21).

Table 21: Duration of isolation – base-case results of original cost–utility model: discharge to community

	Congregate settings				Non-congregate settings			
	Smear grade				Smear grade			
	Negative	Low	High	All grades	Negative	Low	High	All grades
Secondary cases of active TB								
No. of cases	0.0045	0.0126	0.0238	0.0144	0.0015	0.0044	0.0089	0.0051
Costs	£23.87	£67.03	£127.03	£76.82	£8.03	£23.52	£47.26	£27.22
QALY loss								
Morbidity	0.00038	0.00105	0.00200	0.00121	0.00013	0.00037	0.00074	0.00043
No. of deaths	0.00021	0.00060	0.00114	0.00069	0.00007	0.00021	0.00042	0.00024
QALY loss from deaths	0.00377	0.01057	0.02004	0.01212	0.00127	0.00371	0.00745	0.00429
Total	0.00414	0.01163	0.02203	0.01332	0.00139	0.00408	0.00820	0.00472
Secondary cases of LTBI								
No. of cases	0.0997	0.2476	0.2397	0.2057	0.0426	0.1311	0.1256	0.1029
Costs	£23.72	£58.87	£57.00	£48.91	£10.13	£31.18	£29.88	£24.48

	Congregate settings				Non-congregate settings			
QALY loss	0.0036	0.0090	0.0087	0.0075	0.0016	0.0048	0.0046	0.0038
Isolation costs								
14 days' isolation	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424
Reduced isolation	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712
Totals								
Costs saved by reduced isolation	£2,664	£2,586	£2,528	£2,586	£2,694	£2,657	£2,635	£2,660
QALYs forgone by reduced isolation	0.00778	0.02065	0.03077	0.02082	0.00294	0.00886	0.01278	0.00847
ICER	£342,610	£125,223	£82,148	£124,210	£914,940	£299,949	£206,195	£313,975

The number of cases transmitted is low, even for strongly smear-positive patients, and the costs associated with LTBI infections that become active are low because of this and due to discounting (as activation of latent TB may occur in the distant future).

However, the results are sensitive to the assumed infectivity profile of the index case before and after diagnosis. In the most extreme scenario considered (an exponential increase in infectiousness leading up to diagnosis followed by uniform infectivity throughout the 14-day period), enough TB transmission was predicted to reduce costs and QALY losses to the degree that isolation would be considered cost-effective at an ICER of £17,291 and in 98.6% of PSA simulations in patients in congregate settings who are strongly smear positive, and around 63.2% for those at low smear grade. Reducing duration of isolation for smear-negative patients would still result in additional transmission of disease, but the QALY losses estimated are associated with cost savings that are likely to be considered good value for money in all scenarios (all ICERs greater than £50,000 saved per QALY forgone).

In the discharge to ward scenario, isolating all patients with a positive sputum smear is the dominant strategy (is less costly and minimises health loss) and continued isolation of people with a negative smear is also estimated to be good value for money (less than £2000 saved per QALY forgone). The PSA supports this finding (probability of cost effectiveness greater than 85% for all smear grades).

Table 22: Duration of isolation – base-case results of original cost–utility model: discharge to inpatient ward

	Smear grade			
	Negative	Low	High	All grades
Secondary cases of active TB				
No. of cases	0.0684	0.1517	0.3686	0.2270
Costs	£364.28	£808.43	£1,964.26	£1,209.85
QALY loss				
Morbidity	0.00573	0.01271	0.03089	0.01903
No. of deaths	0.00326	0.00723	0.01757	0.01082
QALY loss from deaths	0.05746	0.12751	0.30982	0.19083
Total	0.06319	0.14022	0.34071	0.20985
Secondary cases of LTBI				
No. of cases	1.2084	2.3837	3.0406	2.4971
Costs	£287.35	£566.85	£723.08	£593.82
QALY loss	0.0440	0.0869	0.1108	0.0910
Isolation costs				
14 days' isolation	£5,424	£5,424	£5,424	£5,424
Reduced isolation	£4,560	£4,560	£4,560	£4,560
Totals				
Costs saved by reduced isolation	£212	-£511	-£1,824	-£940
QALYs forgone by reduced isolation	0.10723	0.22711	0.45154	0.30087
ICER	£1,979	dominant	dominant	dominant

6.2.51 Evidence statements

Very low quality evidence from 4 studies suggests that

- Liquid culture test could enable the duration of respiratory isolation to be predicted from pre-treatment sputum smear grade.
- Xpert MTB/RIF based strategy could reduce duration of isolation compared to smear based strategy
- A two-smear approach has potential as a discontinuation strategy of respiratory isolation

Very low quality evidence from 4 studies suggest that factors that prolong or influence time to sputum smear or culture conversion (i.e. a smear/culture positive PTB case who became smear negative after a period of anti-TB treatment) are

- pre-treatment smear grading,
- age,
- miliary,
- >2 zones radiologic involvement,
- cavitation,
- drug resistance, and
- the first two months regimen.

Acceptability/Adverse effects

The body of literature under investigation provided some descriptive statements with regards to adverse effects and were considered as evidence:

"Prolonged isolation occupancy drives increased institutional health care costs through consumption of isolation associated resources, such as isolation room engineering controls and N95 respirators. Perhaps most important…data suggest that isolated hospitalized patients may experience more preventable adverse events, have less care documented, and express greater dissatisfaction with their care." (Lippincot 2013, pg 191)

"Beyond monetary costs isolation may potentially result in decreased vigilance of subjects with respiratory compromise, which can compromise quality of care during the often crucial first few days of hospitalization." (Campos 2008, pg 300)

"Initial masks (high efficiency particulate air HEPA respirators) recommended by CDC were uncomfortable to wear and interfered with patient communication. In addition the masks were reusable but there was no guide as to their lifespan." (Curran 2000, pg 240)

"Longer hospitalizations, decreased provider-patient contact, and potentially suboptimal patient care." (Rakoczy 2008, pg 927)

Health economic evidence

A directly applicable original health economic analysis with potentially serious limitations suggests that, for a patient being discharged to their usual place of residence, the cost effectiveness of isolation is dependent on smear grade and assumed infectivity profile. For patients returning to a shared inpatient ward, 14 days' isolation is the dominant strategy for smear-positive patients, and is cost effective for smear-negative patients. The model demonstrates that smear grading is a potentially useful tool in making the decision to isolate potentially infectious TB patients.

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6.2.61 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that the risk of tuberculosis infection or disease (for example, measured by the number of cases of TB identified against the number of people at risk or tested), the acceptability of approach to those they affect and the risk of exposure (that is, the impact of the intervention on the amount of contact with an infectious patient) were critical for decision making.
Trade-off between benefits and harms	The goal of isolation is to prevent onward transmission of tuberculosis from a patient deemed to be an infection risk. Isolation represents an unusual case where the intervention is performed on the individual but the benefits of the intervention are entirely felt by the wider population, whereas the potential harms of isolation are entirely borne by that individual.
Trade-off between net health benefits and resource use	Negative-pressure isolation, which is indicated for cases suspected to be drug resistant, is very expensive and resource intensive. Side-room isolation, although not negative pressure, is more expensive than standard ward accommodation. The decision problem is therefore how long to isolate a patient in the appropriate setting to minimise his or her infection risk, whilst also ensuring that isolation is not prolonged unnecessarily so as to minimise costs and impact to the patient's quality of life.
Quality of evidence	The de-novo health economic model relies heavily on a single paper for its inputs (Lohmann et al. 2012), which was selected after an exhaustive literature search. The GDG understood that this study had a prominent role in the development of the economic analysis because it provides its results in a helpful level of detail, rather than because it was believed to be especially relevant to the decision context. Whilst it was possible to estimate the burden of disease caused, it was difficult to ascertain the relative proportions of active and latent disease spread by an index case. The ideal source of evidence for a model like this would be one in which people who are known to have active, infectious TB are observed interacting with a population of susceptible people, with the resulting disease transmission recorded and analysed. For evident reasons, no such studies exist. Therefore, the model relies on the significant assumption that people who are being treated for active TB have patterns of relative infectivity that are identical to people who have undiagnosed, untreated TB. By looking at characteristics that, in retrospective studies, are shown to be associated with the transmission of disease in people who did not know they had it, it was inferred that similar factors will influence the spread of disease in people whose TB has been identified (in particular, smear grade and congregate setting – for which attendance or employment at a school was used as a proxy – were considered to be important predictors of transmission risk). The GDG confirmed that this was a reasonable assumption that enabled a potentially informative analysis to be undertaken in a situation where directly relevant evidence does not and will never exist. The model suggests that isolating patients for 2 weeks on standard therapy is unlikely to be cost-effective if they are being discharged home or will be returning to a congregate setting if a QALY is valued at £20,000 and it is assumed that after 14 days of appropriate drug therapy their infectivity drops to zero. Shortening the duration of isolation may incur cost savings, but will also result in QALY losses due to TB related morbidity and associated future treatment. However, these results were sensitive to assumptions made about the infectiousness of the index case prior to diagnosis. In the base case, a uniform rate of infectivity was assumed but the GDG noted that patients may become more infectious as time with TB increases, owing to the development of cavitatory disease, coughing etc. In order to explore this, different infectivity profiles were modelled to reflect a possible peaking of infectiousness around the time of diagnosis. If the profile was assumed to follow an exponential pattern to the point of diagnosis, and then remained at a uniform level consistent with the peak for 14 days, isolation of all smear grades becomes cost-effective (ICER £17,291/QALY) if the patient was subsequently

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	being discharged to a congregate setting. The model also considers a scenario in which a patient is discharged from isolation onto a ward. The Gammaitoni and Nucci equations were used to determine the probability that susceptible patients would be infected with TB if the index case was discharged from isolation onto the ward whilst still potentially infectious. Previous published studies have applied this equation to estimating the spread of TB. Solving these equations required several assumptions to be made which may impact the external validity of the model. A single source of data was used to consider the dimensions of the ward and the number of air changes per hour within it. The number of infectious quanta in the air was sourced from numerous retrospective studies from both human and animal populations but was assumed to be fixed over the course of stay. The number of susceptible patients on the ward was also fixed. All of these parameters will be subject to variability, but there was not sufficient evidence to parameterise this and the mathematical complexity needed was judged to be too great compared to the likely impact on results. The base-case results suggest that isolating patients for 14 days is a dominant strategy for all smear positives, and is cost –effective for smear-negative patients (ICER = £1979/QALY). In a scenario analysis exploring the impact of quanta values on the outcome, the GDG noted that the low values of quanta reported by Riley et. al. (1967) in patients on TB therapy when used in the analysis resulted in isolation for 14 days being cost-effective in only the highest smear-grade patients. It was noted that the quanta rate used in the base case was up to 10 times higher than some reported quanta rates for treated TB patients. However, on balance, the GDG felt that 'true' quanta production rates (in particular, for strongly smear positive patients with other risk factors for isolation) were likely to be higher, not lower, than the figures used and would therefore only serve to make isolation more cost-effective for those patients. Taking into account the assumptions used in the analysis, the data used to parameterise the infectiousness of patients being discharged to congregate (school) or residential settings, the GDG felt that there was insufficient evidence to shorten the duration of isolation in a side room from the recommended 14 days whilst on chemotherapy, but did agree that following 14 days of treatment that it was appropriate to consider discharging the patient from isolation based on a risk assessment and consideration of the discharge destination. The GDG felt that the de-novo analysis and the literature presented put forward a strong case for smear-grading of sputum samples as part of an overall risk assessment of each patient's potential infectiousness. The GDG noted that in some cases this will already be being done, but that there may be issues with regard to no standardised system for smear grading being in place. No specific evidence on the comparative effectiveness of grading systems was considered and this question could therefore not be answered at this time.
Other considerations	The GDG agreed that an important aspect of the relative benefits and harms of isolation has thus far not been considered – namely the health-related quality of life implications of an inpatient isolation spell. Evidence from the literature on short-term isolation (for non-TB reasons) is inconclusive, and patients with MDR TB may require lengths of stay stretching into many months. The GDG felt that a research recommendation to quantify this was therefore appropriate. The GDG noted that evidence in this area would also be of relevance to other areas of the guideline, such as the use of rapid diagnostics for MDR-TB diagnosis, which may shorten unnecessary isolation.

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6.2.71 Recommendations

2 Healthcare settings

114. Care for people with a continuing clinical or public health need for admission with pulmonary TB in a single room (as a minimum) until they have completed 2 weeks of the standard treatment regimen (see section 1.3.2) if they:

- are unlikely to be rifampicin resistant (that is, do not have risk factors for multidrug-resistant TB, or
- have negative rifampicin resistance on nucleic acid amplification test or culture. **[new 2015]**

115. Consider de-escalating isolation after 2 weeks of treatments, taking into account the risks and benefits, if:

- the person is showing tolerance to the prescribed treatment
- there is agreement to adhere to treatment
- there is resolution of cough
- there is definite clinical improvement on treatment; for example, remaining afebrile for a week
- there are not immunocompromised people, such as transplant recipients, people with HIV and those on anti-tumour necrosis factor alpha or other biologics, in the same accommodation
- the person's initial smear grade was not high; for example, 2 or less
- there is not extensive pulmonary involvement, including cavitation
- there is no laryngeal TB. **[new 2015]**

116. Consider discharging from hospital people:

- who do not have a continuing clinical or public health need for admission with pulmonary TB, and
- who are unlikely to be rifampicin resistant (that is, do not have risk factors for multidrug-resistant TB), or
- who have negative rifampicin resistance on nucleic acid amplification test or culture.

If discharged, congregate settings should be avoided for the first 2 weeks of their treatment. [new 2015]

Non-healthcare settings

117. In prisons or immigration removal centres, everyone with X-ray changes indicative of active TB, as well as those with symptoms who are awaiting X-ray, should be isolated in an adequately ventilated individual room or cell. Prisoners and detainees should be retained on medical hold until they have:

- proven smear negative and had a posterior-anterior X-ray that does not suggest active TB, or
- had a negative risk assessment for multidrug-resistant TB and completed 2 weeks of the standard treatment regimen. **[2012, amended 2015]**

Multidrug-resistant TB

118. Consider earlier discharge for people with confirmed multidrug-resistant TB, if there are suitable facilities for home isolation and the person will adhere to the care plan. [new 2015]

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6.2.81 Research recommendations

2 **12. What effects does isolation have on the quality of life of people being treated for**
3 **TB?**

4 ***Why this is important***

5 Isolation is known to significantly affect a person's quality of life. Despite this, the
6 Committee identified no reliable data on the impact of isolation on quality of life . This
7 information is essential in producing economic models that reflect the real costs of
8 isolation. Data on the impact of isolation on quality of life need to be collected and
9 reported.

10

7 Management of latent tuberculosis

7.1 Who should receive treatment for latent tuberculosis infection?

7.1.1 Clinical introduction

Latent TB is defined in this guideline as infection with mycobacteria of the *M. tuberculosis* complex, where the bacteria may be alive but not currently causing active disease. In people with latent TB, the rationale for treating those identified as infected by either Mantoux or IGRAs is to kill any residual dormant bacilli in order to reduce or prevent later reactivation of tuberculosis disease. Single-agent isoniazid has been used in this role for at least 45 years, with considerable data on its efficacy in regimens of between six and 12 months.

In 2005, the Chief Medical Officer's TB Action Plan[hh] set a goal of advising 'on the management of patients requiring preventive chemoprophylaxis'. NICE guidance has attempted to provide such advice with an updated review of evidence in this field for clinicians in England and Wales.

7.1.2 Review question

According to their risk factors, which people with latent TB infection should receive drug treatment to prevent the development of active TB?

7.1.3 Evidence review

The aim of this review was to establish who should, and who perhaps should not, receive treatment for latent tuberculosis infection. To achieve this, the review investigated risk factors that may be associated with a greater potential benefit or harm from the treatment of latent infection. Specifically, this was achieved by attempting to highlight populations that are at highest risk for the progression of latent infection to active disease and may therefore obtain greater benefit from treatment, as well as those that may be at greatest risk from adverse events during treatment and may therefore decide that the potential risks outweigh the potential benefits of treatment.

Papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database) using a focused search strategy. Papers of interest were those examining risk factors for the development of active tuberculosis in those with latent infection, and those examining risk factors for adverse events during treatment for latent tuberculosis. Only cohort (prospective and retrospective), cross-sectional and case-control studies that used multivariate analysis were included. (See appendix C for the full review protocol).

Papers were excluded if:

- they were case studies, case series and narrative reviews;
- they did not include a multivariate analysis;
- the population did not match the population of interest (that is, there was no diagnosis of latent infection by interferon gamma release assay and/or tuberculin skin test); or

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[hh] Department of Health (2004) Stopping Tuberculosis in England: an Action Plan from the Chief Medical Officer. Department of Health: London

- the outcome was not an outcome of interest (that is, progression of latent infection to active disease, or the development of adverse events during treatment).

From a database of 9148 abstracts 99 papers were identified. After ordering full paper copies, 14 papers were included. 1 further paper was identified in the update searches. Relevant data were extracted into evidence tables and GRADE profiles (see appendices D and E).

7.1.47 Evidence statements

Alcohol use

Very low quality of evidence from 1 case-control study of 92 participants with latent tuberculosis infection found that alcohol abuse was associated with significantly higher odds of developing active disease (adjusted OR (95% CI) = 3.8 (1.15 to 12.3)).

However, very low quality evidence from 5 cohort studies with sample sizes ranging from 148 to 3788 was inconclusive about whether or not alcohol use or abuse was associated with an increased risk of adverse events, including hepatotoxicity, during treatment for latent tuberculosis infection. Only 1 of these – a cohort study of 1211 participants from jail or homeless populations – accounted for compliance to treatment. It found no association between excessive alcohol consumption and developing hepatotoxicity (defined as developing a serum concentration of AST ≥2.5 times the upper limits of normal during treatment; adjusted OR (95% CI) = 0.71 (0.43 to 1.17)), as well as a high rate of treatment completion (defined as 60 doses administered within 3 months; adjusted OR (95% CI) = 1.35 (1.04 to 1.76)).

Alanine and aspartate aminotransferase levels

Very low quality evidence from 1 retrospective cohort study of 415 drug users with latent tuberculosis infection found that abnormal baseline ALT levels was associated with significantly higher odds of hepatotoxicity during treatment (adjusted OR (95% CI) = 4.3 (1.6 to 11.4)).

Very low quality evidence from 1 retrospective cohort study of 3377 participants with latent tuberculosis infection found that baseline AST levels above the upper limit of normal was associated with significantly higher odds of hepatotoxicity during treatment (adjusted OR (95% CI) = 5.40 (2.08 to 14.0)). However, very low quality evidence from 1211 participants in jail or homeless populations found that baseline AST levels >2.5 times the upper limit of normal was associated with significantly lower odds of hepatotoxicity during treatment (adjusted OR (95% CI) = 0.72 (0.54 to 0.95)).

CD4 count

Very low quality evidence from 3 cohort studies with sample sizes ranging from 131 to 270 participants was inconclusive about which CD4 threshold represents a useful risk factor for the progression of latent tuberculosis infection to active disease, although there appears to be an increase in risk with decreasing CD4 count.

Diabetes

Very low quality from 1 case-control study of 92 participants found diabetes to be associated with an increased risk of progression of latent tuberculosis infection to active disease (adjusted OR (95% CI) = 5.2 (1.22 to 22.1)).

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Drug use

Very low quality evidence from 2 cohort studies with sample sizes of 148 and 1211 was inconclusive about whether or not illicit drug use, injection drug use or non-injection drug use represents useful risk factors for the development of hepatotoxicity during treatment for latent tuberculosis infection. Only 1 of these – the cohort study of 1211 participants from jail or homeless populations – accounted for compliance to treatment. Very low quality evidence demonstrated no association between injection drug use and developing hepatotoxicity (defined as developing a serum concentration of AST ≥2.5 times the upper limits of normal during treatment; adjusted OR (95% CI) = 2.57 (0.58 to 11.30)), though this may have been driven, to some extent, by the poor rate of treatment completion (defined as 60 doses administered within 3 months; adjusted OR = 0.54 (0.31 to 0.95)).

Ethnicity

Very low quality evidence from 4 cohort studies with sample sizes ranging from 148 to 1211 participants was inconclusive about whether or not ethnicity represents a useful risk factor for the progression of latent tuberculosis infection to active disease or for the incidence of adverse events, including hepatotoxicity, during treatment.

Hepatitis C coinfection

Very low quality evidence from 1 retrospective cohort study of 219 participants found hepatitis C coinfection to be associated with an increased risk of adverse events during treatment for latent tuberculosis infection (adjusted HR (95% CI) = 3.03 (1.08 to 8.52)).

Homelessness

Very low quality evidence from 2 cohort studies with sample sizes of 1211 and 3788 participants was inconclusive about whether or not homelessness represents a useful risk factor for the incidence of adverse events, including hepatotoxicity, during treatment for latent tuberculosis infection.

Incarceration

Very low quality evidence from 2 cohort studies with sample sizes of 1211 and 3788 participants was inconclusive about whether or not incarceration, or previous incarceration, represents a useful risk factor for the incidence of adverse events, including hepatotoxicity, during treatment for latent tuberculosis infection.

Female sex

Very low quality evidence from 4 cohort studies with sample sizes ranging from 148 and 3788 participants was inconclusive about whether or not female sex represents a useful risk factor for the progression of latent tuberculosis infection to active disease or for the incidence of adverse events, including hepatotoxicity, during treatment.

7.1.5 Evidence to recommendations

Relative value of different outcomes	In terms of the present review, the group felt that minimisation of potential harm to the patient from adverse events was the most important outcome. Furthermore, the group also felt that the findings of the health economic modelling allowed them to be confident that all patients who were eligible for latent tuberculosis treatment (those up to the age of 65) would potentially benefit from treatment. Therefore, in weighing up the potential benefits and harms denoted by each risk factor, the group gave greater consideration to the potential harms (the incidence of adverse events) of treatment. In terms of the relative weight given to different adverse events, the group noted

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	that not all adverse events would be severe enough to impact their decision-making. For example, dizziness or itching in the absence of other adverse events may be considered more benign, whereas hepatotoxicity would almost always be cause for concern. In terms of usefulness to their decision-making, the group felt that a useful threshold would be those adverse events that were the primary reason for modifying, stopping or interrupting treatment. For this reason, in considering risk factors for unspecified adverse events, the group gave greater weight to the Pettit (2013) study over the LoBue (2003) study. This was because the Pettit study used the endpoint of 'therapy discontinued due to isoniazid-associated adverse events', whereas LoBue (2003) used 'at least 1 isoniazid-associated adverse event', the majority of which did not impact treatment completion.
Trade-off between benefits and harms	The GDG noted that in deciding whether or not to undergo treatment for latent tuberculosis infection, there is an unusual balance in the potential benefits and harms of the intervention. For most medical interventions, a patient is unwell and an intervention will reduce not only the risk of future morbidity and mortality, but it will also, generally, ease the current burden of disease. In the case of latent tuberculosis infection, the patient is generally 'well', in the sense that the disease has not yet activated. Only a small proportion of patients will actually progress to the active disease, the rest remaining 'well'. Because almost every intervention carries some risk to the patient, for example, in the form of adverse events, this reduction in the potential benefit of undergoing the intervention (which is essentially preventative) means that the decision to do so may be much less clear-cut. The group specified that treatment should be for the close contacts of people who have suspected infectious or confirmed active pulmonary or laryngeal tuberculosis as it is these individuals who pose a risk of infection to their contacts; other sites of disease are not considered to be infectious. Although they also required that there be evidence of latent infection in these individuals, the difficulties in conclusively demonstrating the accuracy of tests for latent tuberculosis (see section 3.1) means that they felt that this additional requirement be added. **Age** Although the varied thresholds used made it difficult to interpret the evidence, the group noted that there is a balance between an increased risk of progressing to active disease and a possible increase in risk of hepatotoxicity as age increases. That the risk of progressing from latent infection to active disease increases with age provides supporting evidence to the new recommendation, based primarily on economic modelling, that everyone up to the age of 65 rather than 35 should be eligible for treatment. **Alcohol use** Again, the group noted that there is a balance between an increased risk of progressing to active disease and a possible increase in risk of adverse events, including hepatotoxicity, as age increases. The evidence for association between alcohol use and the incidence of adverse events was conflicting, though the GDG noted that they had observed an association in their clinical experience. Furthermore, it is known that both alcohol and the antituberculosis drugs used in treatment (isoniazid and rifampicin) are hepatotoxic; therefore an increased risk of hepatotoxicity in those concurrently consuming both is also possible from a theoretical point of view. Due to the conflicting nature of the evidence, the group did not feel that they could explicitly recommend treatment for latent tuberculosis infection (or not) in this population. However, they felt that careful monitoring of this group during treatment would be important, both to ensure adherence to treatment (alcohol misuse has been a barrier to adherence in the group's experience) and to clinically monitor liver function. They also felt that, should they decide against undergoing treatment, this group should be explicitly advised on the risks and symptoms of tuberculosis, to ensure they make a fully informed decision about treatment and

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are aware of the signs of disease progression should it occur.

Alanine and aspartate aminotransferase levels

The GDG noted that, with the exception of 1 study, the evidence generally supported the commonly held view that raised levels of ALT and/or AST (both of which are considered markers of liver function) at baseline is associated with an increased risk of hepatotoxicity during treatment. The exception, Lobato (2005), found that elevated AST at baseline actually *reduced* the incidence of hepatotoxicity. The group speculated that this might have been because the abnormal baseline liver function led to more cautious management of these patients and more careful monitoring of their liver function.

The group felt that the evidence overall, in conjunction with their own clinical experience, supported their recommendation that liver function should be assessed before treatment is initiated, as specified in the British National Formulary. Furthermore, those with abnormal liver function before treatment initiation should undergo more cautious management of their regimen, including careful clinical monitoring. They did not feel that it was strong enough to recommend that people with abnormal liver function not be eligible for treatment.

CD4 count

Again, although the varied thresholds used made it difficult to interpret the evidence, the group noted that there seemed to be a general direction of effect: lower CD4 counts are associated with a higher risk of progressing to active disease. This was supported by the group's clinical experience, as well as from a theoretical perspective (people with HIV or who are immunocompromised, of which CD4 count is a marker, have a decreased immune defence against the infection, making it more likely that the infection will progress to active disease).

The group felt that, because of the increased risk of progression in people with HIV, knowledge of HIV status was key information for a patient to possess in making their decision about whether or not to undergo treatment for latent infection. For this reason, they recommended that patients with risk factors for HIV should undergo HIV testing. They did not feel able to recommend HIV testing for all patients, though they felt that cost-effectiveness data on this would have been useful to their decision-making.

Diabetes

The group noted that there was some evidence that those with diabetes were at increased risk of progressing from latent infection to active disease, though did not feel that necessitated an explicit recommendation that people with diabetes should receive treatment for latent infection. This population is included in the recommendation that anyone under the age of 65 is eligible for treatment for latent tuberculosis infection. The group did, however, feel that these patients should be informed of their increased risk should they decide not to undergo treatment.

Drug use

The GDG noted the lack of evidence relating to the progression of latent tuberculosis infection to active disease in people who misuse drugs.

The group observed that drug use does not appear to increase the risk of adverse events during treatment for latent tuberculosis infection, including that for hepatotoxicity. This was unexpected because they had witnessed an increased risk of hepatotoxicity in these individuals in their own clinical practice and experience. Many drugs are known to have hepatotoxic potential, and therefore, as with alcohol, an increased risk of hepatotoxicity is theoretically feasible in those concurrently taking drugs concurrently with antituberculosis medication. Additionally, there is an increased risk of hepatitis C infection in injection drug users, which could lead to a further risk of hepatotoxicity (see below).

The group discussed the possibility that this finding arose due to poorer adherence to treatment in these patients, or because of more cautious management and supervision of treatment in these patients. The group felt that,

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as with alcohol and those with abnormal baseline liver function, careful monitoring of this group during treatment would be important, both to ensure adherence to treatment and to clinically monitor liver function. This population were also retained in the updated 'inform and advise' recommendation.

Ethnicity

No evidence was found that demonstrated an increased risk of progression from latent tuberculosis infection to active disease or an increased risk of adverse events during treatment based on ethnicity.

Hepatitis C coinfection

The group noted the increased risk of hepatotoxicity during treatment during latent tuberculosis infection. Although the evidence was limited, it is also the experience of the GDG that those at increased risk of tuberculosis infection are at an increased risk of hepatitis B and C, and that this carries an increased risk of drug-induced hepatotoxicity. The group therefore felt that testing those at increased risk of hepatitis coinfection was important, such that informed decisions could be made with regards treatment and that treatment could be carefully managed and monitored if undertaken. They stated, however, that health economic evidence on the testing of all patients with latent tuberculosis infection for hepatitis (and other blood borne viruses) against just testing just those at increased risk of coinfection would have been useful to their decision-making.

No evidence was found that examined the association between hepatitis C coinfection and the progression of latent tuberculosis infection to active disease.

Homelessness

The GDG found the evidence that examined the risk of adverse events during treatment amongst those who are homeless to be inconclusive. There was an increased risk of 'at least 1 isoniazid-associated adverse event', though no link was found to hepatotoxicity. Furthermore, the group felt that homelessness itself was unlikely to lead to any increases in adverse events, rather any increase would be driven by the increased incidence of other risk factors (such as drug or alcohol use) in this population.

None of the studies identified examined the risk of progression from latent tuberculosis infection to active disease in this population.

They felt that the often varied needs of this population means that the linking up of relevant services is important. Diagnosis and treatment should be managed in line with an assessment of the individual's stability, in the context of a more holistic approach that addresses their social needs in addition to their health needs.

Incarceration

None of the studies identified examined the risk of progression from latent tuberculosis infection to active disease in this population.

The GDG found the evidence that examined the risk of adverse events during treatment amongst those who are or who have been incarcerated to be inconclusive. There was an increased risk of 'at least 1 isoniazid-associated adverse event', though no link was found to hepatotoxicity.

Previous positive skin test

None of the studies identified examined the risk of progression from latent tuberculosis infection to active disease in those who had had a previous positive skin test.

1 study examined the risk of hepatotoxicity in this population and found no association. Therefore the group did not feel that a recommendation was needed.

Recent infection

None of the studies identified examined the risk of progression from latent

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	tuberculosis infection to active disease in those who had been infected recently. The group felt that this may have been useful to their decision-making as there is a belief that risk of progression may be greater in the years immediately after infection. **Female sex** No association was found between the risk of progressing from latent tuberculosis infection to active disease and being female. There appeared to be an increased risk of 'any adverse event' amongst women, though not of hepatotoxicity. The group noted that 'normal range' for transaminases in women is in reality lower than it is for men, though gender-specific thresholds to define hepatotoxicity are rarely used in studies. The studies may therefore be underestimating the incidence of hepatotoxicity. However, the GDG did not feel that a recommendation based on the sex of a person with latent tuberculosis infection was appropriate.
Trade-off between net health benefits and resource use	The principal result of the clinical review was to highlight the importance of age in relation to the trade-offs between the risk of progressing to active disease and the risk of hepatotoxicity from LTBI treatment. The GDG referred to this clinical evidence, and it was incorporated into the original health economic analysis described in section 7.2.4 when making these recomendations.
Quality of evidence	The quality of the data for every risk factor for each of the outcomes of interest was 'very low'. The group felt it was important to account for compliance in the analyses, as this would be a major driving or limiting factor for adverse events during treatment and progression to active disease, respectively. However, only 2 studies did this explicitly. The Lobato (2005) study did not do so explicitly, though for each risk factor it reported the adjusted odds ratio for treatment completion, allowing informal comparisons to be made. The group noted that the thresholds used in the evidence for both age and CD4 count vary considerably. This made it difficult to synthesise, interpret, and subsequently operationalise, the evidence as a whole. Common limitations to the evidence base included a failure to report the use of blinding or the reasons for failure to complete treatment, as well as a failure to report the variables used in the multivariate analyses, a lack of information on the treatment regimens used or other care provided, and small sample sizes with small event rates, leading to imprecise estimates of effect.
Other considerations	None.

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7.1.63 Recommendations

See section 7.2.7

7.2 Treatment of latent tuberculosis

7.2.1 Clinical introduction

In people with latent tuberculosis infection, the rationale for treatment is to kill any dormant bacilli in order to prevent later activation of the active disease.

Single-agent isoniazid has been used in this role for many years; a combination of isoniazid and rifampicin has now also entered current practice. Other regimens based on a combination of 2 or more of isoniazid, rifampicin, rifabutin and pyrazinamide are also available. More recently, rifapentine has emerged as a possible candidate in the treatment of latent tuberculosis infection; however, because rifapentine is not licensed in the UK at the time of publication, it cannot be considered for use (although it is included in the evidence base as a comparator.

The aim of this review was to determine which antituberculosis regimen is most effective in treating latent tuberculosis infections, examining available drug monotherapies and combination therapies. These regimens varied in dose, treatment length and type of drug used.

7.2.2 Review questions

For people with latent TB infection in which drug resistance is not suspected, which regimen is the most effective in preventing the development of active TB?

For people with latent TB infection in which drug resistance (excluding MDR- or XDR-TB) is suspected, which regimen is the most effective in preventing the development of active TB?

7.2.3 Evidence review

Papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Review of Effects, and the Health Technology Assessment database) using a focused search strategy to gather all papers relating to the pharmacological treatment of latent tuberculosis. Only randomised controlled trials, quasi-randomised trials and systematic reviews were included. Trials were excluded if:

- it was not possible to separate data for those who were TST- or IGRA-positive for latent tuberculosis;
- the population included people with suspected of multidrug-resistant or extensively drug-resistant infections;
- the studies were non-randomised controlled trials (unless insufficient randomised data identified), observational studies, case series, case studies or narrative reviews.

Subgroups of interest included:

- by age, including people over the age of 35
- people who are immunocompromised or at risk of immunosuppression, including people with HIV

The full review protocol can be found in Appendix C.

From a database of 5385 abstracts, 146 papers were identified following review of their titles and abstracts. After ordering full paper copies, 23 studies were included. Relevant data were extracted into evidence tables (see Appendix ***).

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Where possible, data was synthesised into network meta-analyses using WinBUGS. (For a full description of the network meta-analyses conducted, including both inputs and outputs, see Appendix L).

Where network analysis was not appropriate but there was sufficient data for pairwise meta-analysis, the reviewer used Review Manager to synthesise the data into pooled effect estimates. (For a full description of the evidence synthesis methods, see section ***).

GRADE was used to assess the quality of data for each outcome, and GRADE profiles were generated (see Appendix E). For pairwise comparisons, this followed the format used for other reviews. For network meta-analyses, summary GRADE profiles were generated that appraised the evidence base for each outcome across all possible comparisons.

The quality of the data for each outcome ranged from low to very low, though most outcomes were very low. Overall, common limitations included poor reporting of or a lack of blinding and allocation concealment, a failure to report the approach to randomisation or the definition and method used for outcome measurement, as well as numbers and reasons for loss to follow-up or failure to complete treatment. Furthermore, inconsistency was introduced through the use of DOT (directly observed therapy) for some treatments, and self-administration for others. The evidence base also suffered from considerable imprecision, both in the network meta-analyses and the direct pair-wise comparisons.

All recommendations were formulated using the recommendations made in the previous guideline (CG117) as a starting point.

7.2.41 Health economic evidence

An economic evaluations filter was applied to the search protocol and 730 records returned 3830 records were retrieved. Of these, 3777 were excluded on title/abstract sifting. Of the remaining 50 papers, 3 were included. Evidence profiles are provided in Appendix D.

Holland et al. (2009) used a Markov model to compare 4 regimens for the treatment of LTBI:

1. Self-administered isoniazid daily for 9 months.
2. Directly observed (DOT) isoniazid twice weekly for 9 months
3. DOT isoniazid plus rifapentine once weekly for 3 months
4. Self-administered rifampin daily for 4 months.

In the base-case analysis, subjects were assumed to have newly positive tuberculin skin tests after recent exposure to infectious TB. The baseline activation rate in this cohort was set at 6% over their lifetime. All regimens were dominated by 4R, except 3HRp which was shown to be more effective and had ICERs of $49,997 per QALY compared with 4R and 3HRp and $25,207 per QALY compared with 9H. Given the limited evidence base available to derive point-estimates of the effectiveness of (and associated adherence to) 3HRp3HRp, the authors undertook a sensitivity analysis which showed that, if the risk reduction (for progression to active TB) was less than the base-case estimate of 93% (i.e. less effective than 9H), the ICER crossed their $50,000 cost-effectiveness threshold. In addition, the results were shown to be sensitive to the baseline risk of progression. If the risk of activation is doubled, 4R and 3HRp dominate other options, and 3HRp is more effective than 4R, at a cost of $20,099 per QALY gained. Increasing the risk to 5.2 times the baseline makes 4R and 3HRp equivalent in cost, but 3HRp is more effective. At 10 times the relative risk of disease, 3HRp dominates all strategies.

Shepardson et al (2013) used an individual patient model to compare 9H (self-administered) with 3HRp (DOT). Costs and health outcomes were estimated to determine the incremental costs per active TB case prevented and per QALY gained by 3HRp compared to 9H. The time horizon for the model was 20 years, and all patients were considered at high risk (as defined by CDC guidelines) for developing active TB. In the model, the annual risk of

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progression to active TB was a function of the adherence to treatment, based on an RCT by Sterling et al. (2011) and electronic records on the CDC databases. All 3HRp patients were assumed to receive DOT. In the base-case, the incremental cost per QALY gained for 3HRp compared with 9H is $4565 (95%CI $3584–$5965) from a health system perspective. The cost of rifapentine and the cost of providing DOT are both very influential in determining the cost effectiveness of 3HRp relative to 9H.The base-case analysis uses a rifapentine price less than half the current US wholesale price. At higher risk of progression, 3HRp is found to be increasingly cost effective relative to 9H. Similarly, higher rates of secondary transmission and higher costs of treating TB disease lead to 3HRp being more cost effective relative to 9H.

Diel et al (2001) simulated cohorts of LTBI patients in Germany aged 20 years and 40 years. The baseline lifetime risk of progression to active TB was 6.2%. Costs were taken from a national cost-of-illness study from the German social perspective, which combined inpatient and outpatient costs with indirect costs associated with productivity losses. The intervention was a head-to-head comparison of 9 months' isoniazid compared with no treatment in a population of close contacts of known cases of active TB.

In the base-case, 9H is cost saving. Quality-adjusted life expectancy was slightly extended by 8 days of full health in the lower age group and 7 days in the higher age group, at a cost saving of €417 and €375 per person. In a 'worst-case' analysis (effectiveness of treatment 0.6, isoniazid cost doubled, TB treatment cost halved, probability of reactivation and PPV both at the lower 95% CI), the resulting ICERs were €26,088 and €22,692 per QALY in the 20-year-old and 40-year-old cohorts, respectively. The 9-month course of isoniazid prevention was not attributed a disutility, because the risk of toxic hepatitis as a side-effect was considered very small (0.15% of those completing treatment), and was considered to be more common in age groups outside the two considered. No PSA was undertaken, but a deterministic sensitivity analysis showed that the model is sensitive to treatment cost assumptions (lower 95% estimate reduces the ICER by 41%).

Original health economic modelling

This review question was prioritised for original health economic evaluation by the GDG. A model was produced by Imperial College, London, which compared several treatment regimens for LTBI with no treatment. The patient population considered was individuals who have been diagnosed with LTBI. Four age-groups were considered (17–34 years, 35–50 years, 51–65 years, 66–86 years) because the incidence of adverse events due to treatment is age-dependent, and the lifetime risk of progressing from LTBI to active TB declines with age due to shorter remaining life-expectancy. The relative benefits and harms of treatment are therefore likely to be age dependent and the model was designed to evaluate this. The cohort model runs on an annual cycle for the remaining life expectancy of the cohort, with benefits and costs discounted at 3.5% per annum. The effectiveness and safety of the different regimens considered in the model was evaluated using the outputs of the network meta-analyses of RCTs described in section 7.2.3. Results from the NMAs conducted using a restricted subgroup of evidence most applicable to NHS practice were used in preference to the full dataset.

The model is split into two arms: one in which all patients receive treatment for their LTBI, and a no-treatment arm. In each of these arms, the cohort moves through an identical set of states outlined in Figure 1. Patients may progress to active disease, or remain with latent infection for the rest of their life expectancy. Those who progress to active disease may either die from TB, or survive for until they die of non-TB causes. It is assumed that active cases cause a fixed number of secondary cases, with associated morbidity, mortality and cost impacts.

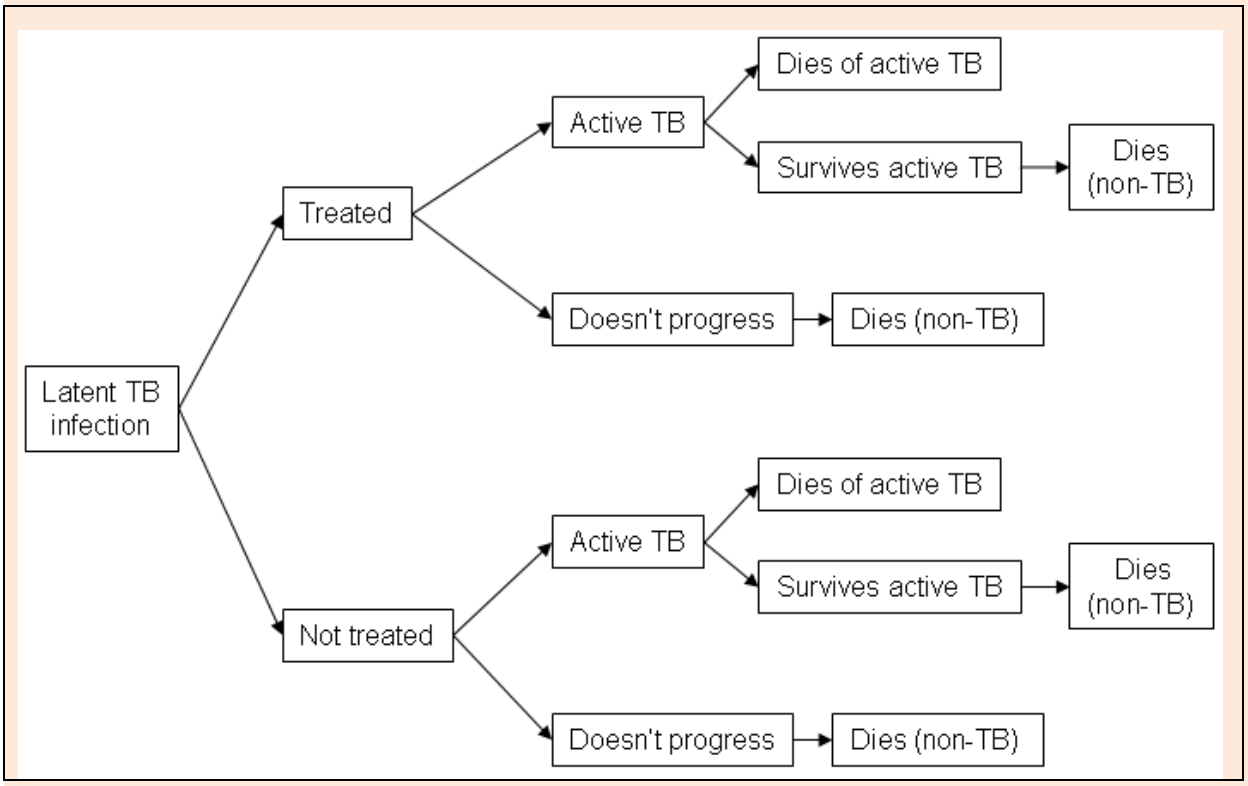

Figure 1: Treatment for latent TB infection – structure of original cost–utility model

The model applies a baseline health-related quality of life weight according to age range (adapted from Kind et al. 1998). Patients who receive treatment for their LTBI have a probability of experiencing treatment related side-effects, namely nausea and vomiting and hepatotoxicity. The GDG provided guidance on the duration of these adverse events (1 week for hepatotoxicity, 2–3 days for nausea and vomiting) with quality-of-life decrements sourced from de Perio et al. (2009) and Nafees et al. (2008) respectively. Patients who progress to active TB experience a QALY decrement due to morbidity and the model calculates QALY losses from TB-related mortality based on age-dependent case-fatality rates taken from Crofts et al. (2008). Costs were considered from an NHS/PSS perspective. Costs of treating adverse events due to LTBI treatment were based on literature and GDG advice regarding healthcare resources required, with costs calculated using NHS reference costs.

A full description of modelling methods and parameters used and their sources is provided in appendix I.

Base-case results

For each age-group and regimen there was an increase in QALYs and costs compared with no treatment – that is, QALYs lost due to treatment-related adverse events were outweighed by QALYs gained by reducing rates of active TB, but the cost of treating LTBI was more expensive than managing future cases of active TB. The results for each regimen compared with no treatment are given for each age stratum in tables 23–26.

Table 23: Treatment for latent TB infection: base-case results of original cost–utility model – age 17–34

Option	Cost (£M)	Total QALYs	Compared with no treatment: Incremental Cost (£M)	Incremental QALYs	ICER (£/QALY)	Numbers of events: Adverse events[a]	Active TB[a]	Secondary cases: Number[a]	Costs (£K)	QALY loss
No treatment	3.00	217,746	-	-	-	-	1175	235	486	32
2RPz	3.76	218,082	0.75	336	2,242	52	47	9	19	1
3HR	5.48	217,918	2.48	173	14,348	112	599	120	245	16
3H	5.97	217,823	2.96	77	38,269	5	918	184	378	25
6H	6.39	217,971	3.38	225	15,033	145	423	85	172	11
12H	9.57	218,012	6.57	266	24,668	360	284	57	115	8
9H	10.00	217,949	6.99	203	34,461	360	497	99	203	13

[a] *undiscounted*

Table 24: Treatment for latent TB infection: base-case results of original cost–utility model – age 35–50

Option	Cost (£M)	Total QALYs	Compared with no treatment: Incremental Cost (£M)	Incremental QALYs	ICER (£/QALY)	Numbers of events: Adverse events[a]	Active TB[a]	Secondary cases: Number[a]	Costs (£K)	QALY loss
No treatment	2.72	182,901	-	-	-	-	882	176	439	29
2RPz	3.80	183,345	1.08	444	2,435	138	35	7	17	1
3HR	5.33	183,131	2.62	230	11,382	116	446	89	221	15
3H	5.74	183,005	3.03	104	29,227	13	686	137	341	22
6H	6.30	183,200	3.58	299	11,969	167	314	63	155	10
12H	9.52	183,254	6.81	353	19,275	394	210	42	104	7
9H	9.89	183,171	7.18	270	26,594	394	370	74	183	12

[a] *undiscounted*

Table 25: Treatment for latent TB infection: base-case results of original cost–utility model – age 51–65

Option	Cost (£M)	Total QALYs	Compared with no treatment: Incremental Cost (£M)	Incremental QALYs	ICER (£/QALY)	Numbers of events: Adverse events[a]	Active TB[a]	Secondary cases: Number[a]	Costs (£K)	QALY loss
No treatment	2.23	139,845	-	-	-	-	593	119	360	24
2RPz	3.86	140,314	1.64	469	3,494	286	23	5	14	1
3HR	5.09	140,090	2.86	245	11,682	122	298	60	180	12
3H	5.37	139,956	3.14	111	28,377	27	460	92	279	18
6H	6.14	140,163	3.92	318	12,330	206	209	42	126	8
12H	9.44	140,219	7.21	374	19,272	453	140	28	84	6
9H	9.72	140,132	7.49	287	26,135	453	246	49	149	10

[a] *undiscounted*

Table 26: Treatment for latent TB infection: base-case results of original cost–utility model – age 66+

Option	Cost (£M)	Total QALYs	Compared with no treatment			Numbers of events		Secondary cases		
			Incremental							
			Cost (£M)	QALYs	ICER (£/QALY)	Adverse events[a]	Active TB[a]	Number[a]	Costs (£K)	QALY loss
No treatment	1.36	79,786	-	-	-	-	292	58	221	15
2RPz	4.52	80,035	3.16	249	12,717	1469	11	2	8	1
3HR	4.69	79,920	3.32	133	24,900	176	145	29	110	7
3H	4.78	79,846	3.41	60	57,082	156	226	45	171	11
6H	6.04	79,958	4.68	171	27,299	551	102	20	77	5
12H	9.54	79,987	8.17	201	40,662	967	68	14	51	3
9H	9.66	79,940	8.30	154	54,042	967	120	24	91	6

[a] *undiscounted*

The base-case results suggest that three regimens, 3HR, 6H and 2RPz, have ICERs below £20,000 per QALY in patients aged 17–65 years, whilst only 2RPz is below this threshold in patients aged 66 years and over.

Sensitivity analysis

Deterministic sensitivity analysis suggests that

- The model is sensitive to the rate at which people progress to active TB, with the value of effective treatment increasing as the progression rate increases. This is logical given the model structure, as at higher progression rates more active TB is avoided in the treatment arm.
- The rate at which people who develop active TB transmit disease to secondary cases is not a significant determinant of cost–utility results.
- The costs of administering LTBI treatment are important: in a scenario in which more intensive follow-up are assumed, ICERs rise substantially.

In a probabilistic sensitivity analysis, 2RPz was cost effective but with considerable uncertainty (maximum probability of being cost-effective of 71%) if the value of a QALY was set at £20,000. No drug regimen was considered cost effective compared with no treatment in the 66+ age group, in whom the risk of progression to active TB is offset by the increased likelihood of adverse treatment related events.

The analysis assumes a fixed number of secondary cases for each untreated active TB case, but does not incorporate further analysis of transmission dynamics. Although general-population-level transmission rates in England are relatively low, the consideration of costs associated with onward transmission beyond the secondary case and the potential for reactivations may alter the relative costs of treatment of current LTBI vs future active disease. This would require further work and the general dynamics of transmission outside south Asian and black African population subgroups are, currently, poorly understood in the UK setting (see section 5.3).

7.2.51 Evidence statements

Development of active TB

Very low quality evidence from a network meta-analysis of 16 RCTs in 74739 participants found 1 month of isoniazid, rifampicin and pyrazinamide to be the most effective intervention in terms of preventing the progression of latent tuberculosis infection to active disease

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(probability best 0.853; median rank 1 (95% CrI 1 to 4)). Very low quality evidence from the same network meta-analysis found placebo or no treatment (probability best 0.000; median rank 15 (95% CrI 13 to 15)) and 3 months of isoniazid (probability best 0.000; median rank 13 (95% CrI 10 to 15)) to be the least effective. This finding – that placebo or no treatment and 3 months of isoniazid were the least effective in preventing progression to active disease – was reflected in the network meta-analysis in the restricted subgroup. There is substantial overlap between the credible and confidence intervals, suggesting good agreement between the network meta-analyses and direct pairwise estimates of effect.

Table 27: Treatment for latent TB infection: development of active TB (full dataset) – rankings for each comparator

	Probability best	Median rank (95%CrI)
1HRZ	0.853	1 (1, 4)
36H	0.087	2 (1, 8)
3RZ	0.028	6 (1, 15)
6HE	0.026	4 (1, 15)
2RZ	0.003	5 (2, 11)
12H	0.001	5 (3, 10)
3HRZ	0.001	8 (3, 13)
72H	0.001	9 (3, 14)
3HR	0.000	8 (4, 12)
3HRp	0.000	8 (4, 13)
6H	0.000	9 (6, 12)
1HR	0.000	12 (5, 15)
9H	0.000	12 (5, 15)
3H	0.000	13 (10, 15)
Placebo / no treatment	0.000	15 (13, 15)

Table 28: Treatment for latent TB infection: development of active TB (restricted subgroup) – rankings for each comparator

	Probability best	Median rank (95%CrI)
2RZ	0.730	1 (1, 6)
3HR	0.153	5 (1, 8)
3HRp	0.077	2 (1, 5)
12H	0.038	3 (1, 5)
6H	0.002	5 (3, 6)
9H	0.000	5 (3, 6)
3H	0.000	7 (6, 8)
Placebo / no treatment	0.000	8 (7, 8)

Adherence

Very low quality evidence from a network meta-analysis of 20 RCTs in 48567 participants (full data set), and another of 9 RCTs in 38543 participants (restricted subgroup), were inconclusive about which intervention was most effective in terms of adherence, although longer, single drug regimens (such as 9, 12 or 72 months of isoniazid – see Tables *** in Appendix D).) appear to perform the worst. The credible and confidence intervals were wide with little overlap in the point estimates for the network meta-analyses and direct pairwise comparisons, suggesting a lack of precision and consistency in the evidence base.

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Table 29: Treatment for latent TB infection: adherence (full dataset) – rankings for each comparator

	Probability best	Median rank (95%CrI)
3HRb	0.459	2 (1, 15)
6HE	0.128	8 (1, 16)
3H	0.125	4 (1, 13)
3HR	0.080	4 (1, 9)
3HRp	0.079	4 (1, 11)
4HR	0.043	7 (1, 14)
2RZ	0.028	6 (1, 12)
3RZ	0.028	9 (1, 15)
3HRZ	0.022	9 (2, 15)
Placebo / no treatment	0.003	8 (3, 13)
4R	0.003	12 (4, 15)
36H	0.003	13 (3, 16)
6H	0.000	9 (5, 13)
12H	0.000	13 (7, 16)
9H	0.000	14 (7, 16)
72H	0.000	16 (13, 16)

Table 30: Treatment for latent TB infection: adherence (restricted subgroup) – rankings for each comparator

	Probability best	Median rank (95%CrI)
2RZ	0.250	4 (1, 10)
3HR	0.200	4 (1, 9)
3H	0.138	5 (1, 10)
4R	0.123	4 (1, 10)
3HRp	0.109	4 (1, 10)
4HR	0.079	5 (1, 10)
Placebo / no treatment	0.067	7 (1, 10)
6H	0.025	7 (2, 10)
9H	0.006	7 (2, 10)
12H	0.004	10 (3, 10)

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Hepatotoxicity

Very low quality evidence from a network meta-analysis of 16 RCTs in 46847 participants (full data set), and low to very low quality evidence from another of 7 RCTs in 37617 participants (restricted subgroup), were inconclusive about which intervention was associated with a lower incidence of hepatotoxicity during treatment, though 3 months of isoniazid and rifapentine perform consistently well. In the restricted subgroup, longer isoniazid-only regimens (9-12 months) and 2 months of rifampicin and pyrazinamide perform poorly, with relatively precise estimates of their low rankings.

Table 31: Treatment for latent TB infection: hepatotoxicity (full dataset) – rankings for each comparator

	Probability best	Median rank (95%CrI)
4R	0.473	2 (1, 6)

	Probability best	Median rank (95%CrI)
3HRp	0.263	2 (1, 6)
3RZ	0.118	6 (1, 13)
6HE	0.058	9 (1, 14)
3HR	0.054	4 (1, 9)
3H	0.013	7 (2, 12)
Placebo / no treatment	0.012	5 (2, 9)
36H	0.006	9 (3, 13)
9H	0.002	6 (2, 12)
3HRZ	0.001	12 (5, 14)
6H	0.000	8 (5, 11)
2RZ	0.000	11 (7, 14)
12H	0.000	12 (7, 14)
72H	0.000	13 (8, 14)

Table 32: Treatment for latent TB infection: hepatotoxicity (restricted subgroup) – rankings for each comparator

	Probability best	Median rank (95%CrI)
3HRp	0.477	2 (1, 4)
Placebo / no treatment	0.290	2 (1, 4)
3HR	0.187	3 (1, 6)
4R	0.045	4 (1, 5)
3H	0.002	5 (3, 5)
6H	0.000	6 (5, 7)
9-12H	0.000	7 (6, 8)
2RZ	0.000	8 (6, 8)

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Rash

Very low quality evidence from a network meta-analysis of 11 RCTs in 14768 participants (full data set) was inconclusive about which intervention was associated with a lower incidence of rash during treatment. It was not possible to construct a network for rash outcome data in the restricted subgroup.

Table 33: Treatment for latent TB infection: rash (full dataset) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo / no treatment	0.331	2 (1, 9)
9H	0.239	3 (1, 9)
6HE	0.156	7 (1, 11)
12H	0.133	4 (1, 9)
3HRp	0.040	5 (1, 11)
36H	0.038	7 (1, 11)
6H	0.025	5 (1, 9)
3HR	0.018	8 (2, 11)
4R	0.017	6 (2, 11)
2RZ	0.002	8 (3, 11)

	Probability best	Median rank (95%CrI)
3RPz	0.000	11 (6, 11)

Nausea and vomiting

Very low quality evidence from a network meta-analysis of 9 RCTs in 5322 participants (full data set), and another of 6 RCTs in 2583 participants (restricted subgroup), were inconclusive about which intervention was associated with a lower incidence of nausea and vomiting during treatment.

Table 34: Treatment for latent TB infection: nausea and vomitting (full dataset) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo / no treatment	0.566	1 (1, 4)
12H	0.392	2 (1, 5)
4HR	0.027	5 (1, 8)
4R	0.011	7 (2, 9)
3RZ	0.002	5 (3, 9)
9H	0.001	8 (3, 9)
6H	0.000	5 (3, 9)
3HR	0.000	5 (3, 9)
2RZ	0.000	7 (3, 9)

Table 35: Treatment for latent TB infection: nausea and vomitting (restricted subgroup) – rankings for each comparator

	Probability best	Median rank (95%CrI)
6H	0.152	3 (1, 6)
3HR	0.170	3 (1, 6)
4HR	0.189	3 (1, 5)
4R	0.048	4 (1, 6)
9-12H	0.002	5 (2, 6)
Placebo / no treatment	0.439	2 (1, 6)

Health economics evidence statement

Evidence from 3 partially applicable CUA studies with potentially serious limitations suggests that the treatment of LTBI in high-risk patients is potentially cost effective compared with no treatment. An original, directly applicable model with minor limitations suggests that treating patients with LTBI is potentially cost effective compared with no treatment in all patients under 65 years of age, after which the balance between benefits and harms of treatment becomes less favourable, and QALY gains are insufficient to counterbalance the costs of treatment. All of the models considered show sensitivity to the progression rate to active TB, adverse event rates, and cost of treatment parameters.

7.2.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the relative importance of the outcomes and agreed that progression to active tuberculosis, adherence and adverse events, particularly those that are severe enough to require a modification,

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	interruption or discontinuation of treatment, were critical for decision making. The group discussed which adverse events were likely to meet the criteria specified above, and agreed that treatment-related mortality, hepatotoxicity, rash, allergy and nausea and/or vomiting were potentially useful to their decision-making. They also noted that in deciding whether or not to undergo treatment for latent tuberculosis infection, there is an unusual balance in the potential benefits and harms of the intervention. For most interventions, a patient is unwell and an intervention will reduce not only the risk of future morbidity and mortality, but it will also, generally, ease the current burden of disease. In the case of latent tuberculosis infection, the patient is generally 'well', in the sense that the disease has not yet activated. Only a small proportion of patients will actually progress to the active disease, the rest remaining 'well'. Because almost every intervention carries some risk to the patient – for example, in the form of adverse events – this reduction in the potential benefit of undergoing the intervention (which is essentially preventative) means that the decision to do so may be much less clear-cut. For this reason, outcomes such as hepatotoxicity (and other severe adverse events) are particularly important as the intervention is being given to people who are otherwise 'well'. Although specified in the protocol as important, during their discussion of the evidence the group noted that, in their experience, nausea and vomiting as an adverse event during treatment for latent tuberculosis infection is very rare. If it at all, it would occur only in the first couple of days and would not lead to cessation of treatment. This is supported in the evidence in that there was generally insufficient event rates to achieve a significant effect (in the pairwise comparisons, at least).
Trade-off between clinical benefits and harms	The treatment of LTBI involves several potential trade-offs. If a patient is diagnosed as LTBI positive, their lifetime risk of progression to active infectious tuberculosis needs to be weighed against their potential loss of health due to treatment related adverse events. LTBI is an asymptomatic condition and the patient may feel otherwise well. An additional benefit of LTBI treatment is preventing the development of infectious TB which may be transmitted to others in the future. Therefore, a patient treated for LTBI may be exposed to treatment-related harms that are offset not only by that person's own benefits (in avoiding active TB with its associated impact on quality of life and life expectancy), but also by benefits to others who avoid morbidity and mortality. The health economic model provided an approximate quantification of this additional benefit by assuming a fixed number of secondary cases are associated with activation of disease. Previous guidance had considered that hepatotoxic adverse events were sufficiently common and serious compared with the risk of progression to active TB that treatment for LTBI was not recommended in patients older than 35 years. The original economic model used evidence identified in section 7.1 to estimate the relative likelihood of hepatotoxicity in people of various ages (Smith et al. 2011), and also estimated the costs and decrement to quality of life that would be expected from hepatotoxic events. These were balanced against the benefits of treatment in preventing active TB (and its onward transmission). This analysis showed that the benefits of LTBI treatment can be expected to outweigh the risks at all ages up to 65, rather than 35 years. Evidence used in the original model suggested that people who develop active TB at an older age are more likely to die of it (Crofts et al. 2008). Consequently, the model reflects that people aged 51–65 are approximately 5½ times more likely to develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to die of active TB, if they develop it, than people aged 15–44. This proved to be an important consideration in balancing the risks and benefits of treatment in people of different ages; it is

	not clear that previous analyses have adequately accounted for this trade-off. Although children were not explicitly covered by the model, and limited clinical evidence was identified, the GDG felt that treatment of latent infection in children was justified. This was because the rate of progression from latent infection to active disease is known to be high in children (and the model clearly demonstrated that the higher the rate of progression, the more cost-effective the decision to treat). Furthermore, the risk of hepatotoxicity is believed to be lower in children. In this way, children represent a group for which the potentrial benefits of treatment are high, and the potential harms of treatment are low. The marketing authorisation for pyrazinamide only specifies that it is suitable for treatment of active TB; therefore, use as chemoprophylaxis in people with LTBI would be off-label. The GDG noted that, in the health economic model, 2RPz emerged as the most cost-effective treatment regimen; however, the clinical experience of the group agreed with the finding that pyrazinamide is the most hepatotoxic of the drugs considered. Therefore, the group felt that it would not be appropriate to recommend off-label prescribing when safer licensed alternatives exist.
Trade-off between net health benefits and resource use	The GDG's discussions mostly concentrated on the original analysis that had been developed for this guideline, as the 3 published cost–utility analyses that were identified had different objectives and conclusions. Only 1 of the analyses included a no-treatment option, concluding that preventative treatment is likely to be cost saving. Two of the analyses provided some support for the use of a short regimen containing rifapentine. As rifapentine is not currently licensed in the UK, the GDG was unable to recommend this approach; however, they noted that this evidence was broadly supportive of shorter regimens containing rifamycins. For its estimates of efficacy and safety, the original model relied on results from the NMAs conducted using a restricted subgroup of evidence most applicable to NHS practice, in preference to those derived from the full dataset. This was because these results were judged to be most applicable to the GDG's decision-making and also because there were some inconsistencies in the NMAs based on the full dataset (for example, the point-estimate for rate of TB activation in people taking 9H was less than that for people taking 3H but greater than that in people taking 6H). These results were entirely consistent with simple random error in (that is, credible intervals were wide and overlapping), and the GDG was aware that this imprecision would be appropriately accounted for in probabilistic modelling. However, the GDG also knew that the model's deterministic base case would be based on the expected values of these parameters, and were concerned that this might lead to results that would be difficult to explain. The GDG noted that the evidence synthesis from the restricted subgroup of more applicable studies did not have this feature, and represented all treatments they were likely to consider, so they chose to prefer this evidence. In presenting results, a departure was made from the usually recommended practice of comparing each possible option to the next-cheapest non-dominated strategy (that is, a 'fully incremental' analysis). Instead, all options were compared with a common baseline of no treatment. This was because the GDG recognised – in line with conclusions elsewhere in this review and section 6.1 – that not all options would be appropriate for all people. Under this circumstance, it is possible to present a series of incremental analyses in which 1 or more options have been excluded; however, this would have entailed a lengthy series of analyses that would be laborious to follow and would, in this case, result in identical conclusions to the simpler approach of comparing everything to a common baseline. In its deterministic base case, the model suggested that treating all people under the age of 65 with 6H or 3HR would lead to net health gain at a cost of less than £20,000 per QALY gained, compared with no treatment. The

	balance of benefits, harms and costs was less favourable in people over the age of 65: ICERs exceeded £20,000 per QALY for all regimens other than 2RPz, which the GDG thought would be inappropriate to prescribe to asymptomatic people, especially those in an older age-group. For this reason, the GDG concluded the most appropriate recommendation would be to offer treatment with 6H or 3HR to all people with LTBI under the age of 65. The GDG spent significant time discussing the most appropriate number to use for its base-case estimate of activation rate in people with untreated LTBI. It concluded that the best source of information would be a pooled estimate of the activation rate in placebo arms of included RCTs: 0.00196 cases per patient-year (95%CrI 0.0003 to 0.0127). However, the GDG noted that this was probably quite a conservative estimate, as the RCTs had recruited participants in a variety of ways (including some forms of non-targeted screening), and would therefore feature a good proportion of cases of long-dormant LTBI that would be unlikely to become active. In contrast, the contexts in which diagnosis is carried out in England and Wales tend to be associated with an increased probability of disease activation (for example, in children, in people who are immunocompromised and in people who have been identified as contacts of recent, confirmed cases of active TB). For this reason, the GDG felt that the analysis provided a lower bound to the plausible cost effectiveness of LTBI treatment in the NHS setting. As could be predicted, the model demonstrated conspicuous sensitivity to this number. If the rate of activation was lower than the base-case estimate, it quickly became poor value to offer any kind of treatment to people with LTBI. Conversely, if the activation rate was increased, the net benefit of treatment became much higher. The relationship between the 2 regimens favoured by the GDG – 3HR and 6H – did not change much as this parameter was varied over a plausible range: as it increased to levels above the base-case value, 6H began to gain a small advantage over 3HR, though results remained comparable. The GDG was aware that the base-case results relied on cost estimates that assumed a limited amount of healthcare professional involvement in the follow-up of people taking chemoprophylaxis. Under an alternative assumption, in which much more intensive follow-up was simulated, the model suggested treating people for LTBI would be much less cost effective.
Quality of evidence	Only 1 of the identified studies was carried out exclusively in children. This study suffered from a number of methodological limitations, including a lack of blinding, poor definition of outcome and unclear method of outcome measurement, early termination of the trial, evidence of differences in the care provided to each of the intervention groups, a lack of information on the comparability of groups at baseline, retrieval of data 'second-hand' from records and databases, and considerable irregularity in drug intake. Other than this, it was not possible to separate any data in children and young people from that for adults. For this reason, no subgroup analyses based on age were conducted. It was not possible to construct a network for rash outcome data in the restricted subgroup. The quality of the data for each outcome ranged from low to very low, though most outcomes were very low. Overall, common limitations included poor reporting of or a lack of blinding and allocation concealment, a failure to report the approach to randomisation or the definition and method used for outcome measurement, as well as numbers and reasons for loss to follow-up or failure to complete treatment. Furthermore, inconsistency was introduced through the use of direct observation for some treatments, and self-administration for others. The evidence base also suffered from considerable imprecision, both in the network meta-analyses and the direct pair-wise comparisons.

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	The generalisability of the 'full data set' network meta-analyses to the UK context is, in theory, more limited than that of the restricted subgroup due to the inclusion of data from high incidence countries and data from studies exclusively in people with HIV. However, in reality, the broad patterns that emerged from the analysis of the full data set were very similar to those that emerged from the subgroup sensitivity analysis. There is substantial overlap between the credible and confidence intervals for the progression to active tuberculosis, rash and nausea and vomiting analyses, suggesting good consistency between the direct and indirect pairwise estimates of effect. The credible and confidence intervals for adherence and hepatotoxicity were wide with little overlap in the point estimates for the network meta-analyses and direct pairwise comparisons, suggesting a lack of precision and consistency in the evidence base for these outcomes.
Other considerations	

7.2.72 Recommendations

119. Be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who:

- are HIV positive
- have excessive alcohol intake
- are injecting drug users
- have had solid organ transplantation
- have a haematological malignancy
- have had a jejunoileal bypass
- have diabetes
- have chronic renal failure or receive haemodialysis
- have had a gastrectomy
- are having anti-tumour necrosis factor-alpha treatment or other biologic agents
- have silicosis.

People in these groups who do not have treatment for latent TB, as specified in recommendations 120 to 127, for any reason should be advised of the risks and symptoms of TB (on the basis of an individual risk assessment), usually in a standard letter of the type referred to as 'Inform and advise' information, and have posterior-anterior chest X-rays 3 and 12 months later. [new 2015]

120. For people, including those with HIV, aged younger than 65 years with evidence of latent TB who have been in close contact with people who have suspected infectious or confirmed active pulmonary or laryngeal drug-sensitive TB offer either of the following drug treatments:

- 3 months of isoniazid and rifampicin, or
- 6 months of isoniazid. [new 2015]

121. For adults between the ages of 35 and 65 years, offer drug treatments only if hepatotoxicity is not a concern. [new 2015]

122. Base the choice of regimen on the person's clinical circumstances. Offer:

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- 3 months of isoniazid and rifampicin if hepatotoxicity is a concern; this would include both liver function (including transaminase) tests and assessment of risk factors
- 6 months of isoniazid if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant. [new 2015]

123. Clearly explain the risks and potential benefits of each treatment regimen. In discussion with the person, select a suitable regimen if they wish to proceed with preventive treatment. [new 2015]

124. Offer testing for HIV and hepatitis B and C before starting treatment for latent TB. For recommendations on hepatitis B and C, see NICE guidelines on Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults. For recommendations on HIV, see NICE guidelines on Increasing the uptake of HIV testing among black Africans in England and Increasing the uptake of HIV testing among men who have sex with men. [new 2015]

125. If a person also has severe liver disease, for example, Child-Pugh level B or C, work with a specialist multidisciplinary team with experience of managing TB and liver disease. [new 2015]

126. Manage treatment with caution, ensuring careful monitoring of liver function, in:

- people with non-severe liver disease
- people with abnormal liver function (including abnormal transaminase levels) before starting treatment for latent TB infection
- people who misuse alcohol or drugs. [new 2015]

127. Ensure people having treatment for latent TB who also have social risk factors, such as misusing alcohol or drugs or being homeless, are linked to support services. They should also have an assessment of social needs and stability, including potential barriers to adherence or treatment completion. [new 2015]

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7.2.8 Research recommendations

13. For people with latent TB, are shorter regimens effective in preventing the development of active TB? If so, which regimen is the most effective?

Why this is important

Shorter regimens with minimal side-effect profiles would help encourage people with latent TB to have and adhere to treatment. Randomised controlled trials comparing the effectiveness of shorter regimens, such as those containing rifabutin or rifapentine, with the current standard regimen (6 month of isoniazid and 3 month of isoniazid and rifampicin) in preventing the development of active TB are needed. Measurements are also needed of the incidence of adverse events, particularly hepatotoxicity. The systematic reviews for this guideline noted the increased risk of hepatotoxicity associated with pyrazinamide-containing regimens. Given this, the Committee , did not feel that these regimens need be investigated further. Trials would need to be of sufficient size to take into account the low rate of progression from latent to active TB.

8 Prevention and control

8.1 BCG vaccination – overview

8.1.1 Clinical introduction [2011]

Bacille Calmette-Guerin (BCG) was developed by Calmette and Guèrin, at the Pasteur Institute (Lille) using *in vitro* attenuation by repeated passage of an isolate of *M. bovis* from 1908 onwards; it was finally tested in humans in 1921. Since BCG has never been cloned and has been grown under different conditions and in different laboratories, genetic differences have developed between the various commercially used strains,{279} so called 'antigenic drift'. Genome research has since shown that in the passaging of the organism, but before its distribution from the Pasteur Institute, a section of the genome, the RD1 region, was deleted. This deleted region common to all BCG strains contains antigens such as ESAT6, CFP10 and tb7.7 which are now used in interferon-gamma based blood tests, and hence these blood tests are not affected by prior BCG vaccination (see section 5.1 for further details).

The efficacy of a vaccine is a measure of its activity on individuals given the vaccine and can be defined as the proportion of those vaccinated who gain protective immunity from the vaccination.{280} Huge variations in estimates of efficacy against pulmonary TB, ranging from 0% to >80%, have been shown for different BCG vaccines in various geographical settings.

While a number of explanations have been put forward for this, geographical latitude seems to have a particularly important effect, accounting for over 40% of the variability in efficacy.{281} Thus nearly zero efficacy against tuberculosis in India,{282} is contrasted with a 64% protective efficacy in people of Indian origin with the same vaccine in a higher, more temperate, latitude.{283} Though the effect of climate on environmental mycobacteria has been suggested as the cause of the latitude effect, this has not been proven.

A further conundrum in BCG efficacy is that even in parts of the world where there is little reported efficacy against tuberculosis, efficacies of 50–60% are reported against leprosy and Buruli ulcer, caused by other mycobacteria.{280} Yet another problem with interpreting the data is that although it was assumed that the tuberculin sensitivity induced by BCG vaccination correlated with protective efficacy, this is not so. In a large UK study there was no correlation between tuberculin sensitivity induced by BCG and protective efficacy; those individuals tuberculin negative after BCG vaccination derived just as much protection as those who became tuberculin positive.{284}

Many controlled trials have followed efficacy for 10–15 years and have shown some decline over time, but the total duration of any benefit was not known and could only be expressed as an efficacy lasting up to 15 years.{285} The only truly long-term follow-up of BCG vaccination, in a North American aboriginal population, reported in 2004, showed 50% protective efficacy lasting for at least 50 years.{286}

BCG is a live vaccine and as such is contraindicated{3} in a number of situations where the immune system may be compromised, particularly if the person is known or suspected to be HIV positive, because of the risk of generalised BCG infection. HIV testing, after appropriate counselling, is also an important consideration, but lies outside the scope of this guideline. Readers should be aware of the British HIV Association guidelines on TB/HIV co-infection{8} and those forthcoming on testing from the British Association for Sexual Health and HIV.

Current practice in vaccination is led by the advice of the Joint Committee on Vaccination and Immunisation, principally through the 'Green Book'.{3},{21}

8.1.2 Recommendations

128. To improve the uptake of BCG vaccination, identify eligible groups (in line with the Department of Health's Green Book) opportunistically through several routes, for example:

- new registrations in primary care and with antenatal services
- people entering education, including university
- links with statutory and voluntary groups working with new entrants and looked-after children and young people
- during contact investigations. **[new 2015]**

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129. When BCG is being recommended, discuss the benefits and risks of vaccination or remaining unvaccinated with the person (or, if a child, with the parents), so that they can make an informed decision. Tailor this discussion to the person, use appropriate language, and take into account cultural sensitivities and stigma. [2006]

130. If people identified for BCG vaccination through occupational health, contact tracing or new entrant screening are also considered to be at increased risk of being HIV positive, offer them HIV testing before BCG vaccination[ii]. [2006]

8.2 BCG vaccination - For neonates [2011]

8.2.1 Clinical introduction

Neonatal BCG (up to age three months) is given in countries, or in subgroups defined by ethnicity and/or deprivation, with high rates of TB disease. Efficacy studies on neonatal BCG have used different end points which have contributed to some confusion about its efficacy in various settings. These have included the end points of pulmonary disease, death, TB meningitis, disseminated (miliary) disease, and laboratory-confirmed cases.

In England and Wales, which has had a selective neonatal BCG programme for over 20 years, assessments of coverage of appropriate infants have shown substantial variation in, and deficiencies in, both BCG policy and implementation.{287} These deficiencies and system problems were particularly in medium and low TB incidence districts which often had no system for identifying those neonates for whom BCG was recommended.

8.2.2 Current practice

The DH advises BCG vaccination for all neonates at higher risk of TB, with opportunistic vaccination of older children as necessary, according to criteria set out below in the recommendations.

The review of current services, conducted in the year prior to the introduction of neonatal vaccination and abolition of school-based vaccination, found that outside London, only two of 62 clinics (3%) (in the same HPU, an area of high notifications) reported universal neonatal BCG vaccination. In London, 12 of 31 clinics (39%) reported universal coverage. There was no consistency in the risk groups used for selected neonatal BCG. Many respondents did not

[ii] See the British HIV Association guideline for details of further action in HIV-positive patients.

name any explicit risk groups, but those who gave details mostly cited ethnicity, immigration and family history as the means for identifying neonates at higher risk.

8.2.3 Methodological introduction

Studies investigating the effectiveness of BCG vaccination administered in neonates and infants in preventing the development of TB infection or disease were sought. This was compared to unvaccinated groups in relevant populations. One meta-analysis, one cohort study and one case control study were found.

One meta-analysis conducted in the USA{288} included five RCTs and 11 case control studies in the analysis. The scope was international, but all RCTs were conducted in the northern hemisphere and were situated far from the equator relative to case controls, which were distributed across both temperate and equatorial regions. The analysis combined RCT and case control studies separately and did not use cross-design analysis since there were too few RCTs relative to case control studies. It was therefore appropriate to grade the evidence statements according to whether they were derived from the RCT (level 1) or case control results (level 2).

Factors for consideration raised by the meta-analysis included the following:

- The duration of BCG vaccination protection administered in infancy was inadequately established despite information on this issue being available from six studies. This was due to the small numbers of TB cases when data was analysed separately by year of occurrence.
- The impact of BCG strain on efficacy of immunisation was not associated with variation in the protection afforded by the vaccine in the studies reviewed.
- Differences in the characteristics and methodological quality of individual studies were addressed by a sensitivity analysis, expressed as a study quality validity score.
- Study quality validity scores accounted for 15.3% of the heterogeneity in the results of the nine case control studies, while RCTs were homogeneous.
- Distance from the equator did not appear to be an important correlate of BCG efficacy reported by case control studies, while RCTs displayed homogeneity in terms of distance from the equator.

One cohort study conducted jointly in the Federal Republic of Germany (FRG) and the German Democratic Republic (GDR),{289} was published prior to the meta-analysis, but not cited in it. The study retrospectively focused on BCG vaccination administered to an entire population of neonates in the GDR over a three and a half year period compared to no vaccination in the FRG over the same time period to investigate the efficacy of the vaccine in preventing cases of TB meningitis.

A case control study conducted in Spain,{290} which was not cited in the meta-analysis was excluded due to methodological limitations presented in Appendix N.

8.2.4 Evidence statements

Evidence was found for the efficacy of BCG vaccination in infancy for preventing:

- pulmonary TB disease
- TB deaths
- TB meningitis
- laboratory-confirmed TB cases
- disseminated TB.

Evidence for these five outcomes is presented in Table 34.

Table 34: Summary of evidence: neonatal BCG vaccination

Outcomes	Intervention: BCG vaccinated *vs.* unvaccinated infants	Results	Association/statistical significance	Ref and NICE grade
Pulmonary TB disease	Four RCTs	Protective effect 0.74	Combined RR 0.26 (95% CI 0.17 to 0.38, p< 0.05)	{288} 1+
	Nine case control studies	Protective effect 0.52	Combined OR 0.48 (95% CI 0.37 to 0.62, p<0.05)	{288} 2+
TB deaths	Five RCTs	Protective effect 0.65	Combined RR 0.35 (95% CI 0.14 to 0.88, p<0.05)	{288} 1+
TB meningitis	Five case control studies	Protective effect 0.64 (based on 181 cases of TB meningitis)	Combined OR 0.36 (95% CI 0.18 to 0.70, p<0.05)	{288} 2+
	One cohort study	0/770,000 intervention *vs.* 57/2,100,000 (0.0048%) control cases developed TB disease	Not reported	{289} 2+
Laboratory-confirmed TB cases	Three case control studies	Protective effect 0.83 (based on results of 108 TB cases confirmed by either histology or culture)	Combined OR 0.17 (95% CI 0.07 to 0.42, p<0.05)	{288} 2+
Disseminated TB	Three case control studies	Protective effect 0.78	Combined 0.22 (95% CI 0.12 to 0.42, p<0.05)	{288} 2+

8.2.52 Health economics

The GDG considered the interactions between neonatal and school-age BCG vaccination programmes required population dynamic economic modelling, which is, at the time of writing, being commissioned by the DH. With this in mind, recommendations on neonatal BCG are presented purely on the basis of clinical evidence, pending the findings of the model.

8.2.68 From evidence to recommendations

Neonatal BCG is significantly better than no vaccine using the end points of pulmonary disease, death, meningitis, laboratory-confirmed TB and disseminated TB.

There is difficulty ensuring thorough vaccination coverage in primary care, where babies are not registered until the first appointment, compared to vaccination by midwives, for example, where coverage can be assured.

The GDG supported the explicit criteria set out by the WHO for discontinuing universal vaccination, but wished TB clinicians and service planners to be aware of possible future

changes to the criteria in response to changing global epidemiology. The aim of this section is to guide clinicians in vaccinating those who are most at risk.

Given the conclusions of the health economics for school-based BCG vaccination in section 11.3, the recommendations seek to provide guidance for a neonatal BCG programme that will offer protection to all who are at risk. In a high-incidence area, this may be most easily provided by a universal programme.

The largest group of neonates who are at increased risk of TB are those whose families have immigrated from high-incidence countries. Neonates continue to be at risk even if their parents were also UK born because of continuing migration, home visits and exposure to increased levels of TB within communities. The recommendations therefore advise selection on the basis of a parent or a grandparent being born in a high-incidence country. GDG members were aware of selection being practised on the basis of skin colour or surname, and aimed to provide clear-cut recommendations to replace these practices.

In accordance with the Green Book,[{3}] tuberculin skin testing is not routinely recommended prior to BCG vaccination for children under six years of age.

8.2.7 Recommendations

131. Discuss neonatal BCG vaccination for any baby at increased risk of TB with the parents or legal guardian. [2006]

132. Primary care organisations with a high incidence of TB should consider vaccinating all neonates soon after birth. [2006]

133. In areas with a low incidence of TB (see Public Health England's tuberculosis rate bands), primary care organisations should offer BCG vaccination to selected neonates who:

- were born in an area with a high incidence of TB, or
- have 1 or more parents or grandparents who were born in a high-incidence country, or
- have a family history of TB in the past 5 years. **[2006]**

8.3 BCG vaccination - For infants and older children

8.3.1 Clinical introduction

Following clinical trials in the early 1950s, BCG vaccination was introduced for previously unvaccinated adolescents aged 10–14.{284} Age 10–14 was selected for vaccination in 1953 because at that time, in what was nearly entirely a white UK-born population, TB was most common in those aged 15–29 (with a second peak in older people). This cohort, now aged over 70, have the highest TB rates among white UK-born people (see Appendix K). The rationale therefore was to give vaccination at this age to try to prevent acquisition of pulmonary disease before this peak, and it became known as the 'Schools BCG Programme'. During the writing of this guideline, the DH abolished the programme, replacing it with neonatal vaccination based on the criteria given above.

Tuberculosis rates fell through the 1950s and early 1960s by almost 10% per annum, and continued to fall at a lower rate until 1987 (approximately), since when there has been an increase. However, over this time, both the proportion of cases and rates of disease in the white UK-born ethnic group have continued to fall. The proportion of cases in this ethnic

group was 85% in 1985, 43% in 1993, 37% in 1998, and is now under 30%.{140} Rates of TB in white UK-born children aged 10–14 years, the cohort of previously unvaccinated children to whom the schools programme applies, are between one and two cases per 100,000 for both sexes (see Appendix K).

International criteria for discontinuation of unselective BCG vaccination

The International Union against Tuberculosis and Lung Disease published their criteria for discontinuation of BCG programmes in countries of low prevalence in 1993.{291} This set out general considerations and criteria. The general criteria to be met in a country before stopping or modifying BCG programmes were:

- there is a well functioning TB control programme
- there has been a reliable monitoring system over the previous five years or more enabling the estimation of the annual incidence of TB by age and risk groups, with particular emphasis on TB meningitis and sputum smear-positive pulmonary TB
- due consideration has been given to the possibility of an increase in the incidence of TB resulting from HIV infection.

The criteria for discontinuing a BCG vaccination programme in a country with a low prevalence of TB were:

- the average annual notification rate of sputum smear-positive pulmonary TB should be five cases/100,000 population or less during the previous three years, or
- the average annual notification rate of TB meningitis in children under age five years of age should be less than 1 case per 10 million general population over the previous five years, or
- the average annual risk of TB infection should be 0.1% or less.

Additional considerations were also suggested.

Cost: with it being advisable, but not essential, to calculate the number of cases which would be prevented by continuing BCG vaccination, so that the saving can be expressed in terms of preventing human suffering and also in saving of cost of treatment.

Adverse reactions to BCG: documentation of the rate of adverse reactions to BCG vaccination in a country are helpful. A low incidence rate of active tuberculosis, coupled with a high rate of adverse reaction tends to reinforce a decision to stop or modify the BCG vaccination programme. The reported rates of serious adverse reactions varies from country to country, with vaccination technique used, the preparation of BCG vaccination used, and doctors' awareness of reactions being factors influencing the reported rates.

Risk groups: in the event of discontinuation of the BCG vaccination programme for the general population, it may be advisable to continue vaccination in certain well-defined population groups with a known high notification rate of active tuberculosis.

8.3.2 Current practice

The Department of Health no longer recommends BCG vaccination for school children between ages 10–14 years.

8.3.3 Methodological introduction

The focus was on studies investigating the effectiveness of BCG vaccination administered in a school-aged population in preventing TB infection or disease. One RCT and two cohort studies were found that addressed the topic.

One RCT conducted in the UK{285} reported on the protective efficacy of BCG vaccination against tuberculosis (TB) disease in vaccinated and unvaccinated groups of school-aged

subjects in England over a 20-year follow-up period. Two cohort studies, both conducted in the UK,{292},{293} retrospectively identified notified cases of TB disease who had been eligible for BCG vaccination within the schools vaccination scheme when aged 13.{292},{293} These studies estimate the protective efficacy of the BCG vaccine in this general population and in the white ethnic group. Sutherland and Springett{292},{293} estimate the numbers of additional TB notifications that would be expected among young white adults annually, if the schools BCG scheme were to be discontinued at specific dates. Both cohort studies incorporated data from the RCT cited above.

8.3.49 Evidence statements

Efficacy of BCG vaccination for preventing TB disease

One RCT{285} and one cohort study{292} found that BCG given in school-aged children led to a reduction in the annual incidence of TB disease in vaccinated compared to unvaccinated individuals. Evidence is presented in Table 35.

Table 35: Summary of evidence: vaccinated and unvaccinated children of school-going age

BCG vaccinated *vs.* unvaccinated results	Statistical significance	Ref and NICE grade
Protective efficacy 0.77; average annual incidence 0.23 per 1,000 versus 0.98 per 1,000 (20 years follow-up)	Not reported	{285} 1+
1949–1981: Protective efficacy 0.80 (ages 15–19), 0.75 (ages 20–24)	Not reported	{292} 2+
1983: Protective efficacy 0.75 (ages 15–24); notification rate 3.3 per 100,000 versus 13.2 per 100,000	Not reported	{292} 2+

BCG vaccination in school-aged children and longitudinal trends in TB prevention

Evidence was found on BCG vaccination use in school-aged children in England and Wales and the following longitudinal trends:

- decrease in the efficacy of BCG and the incidence of TB notifications
- the estimated risk of notified TB in the white ethnic population eligible for the school's BCG vaccination scheme
- TB notifications prevented by BCG vaccination in the white school-aged population
- TB notifications as a consequence of discontinuing the BCG schools vaccination scheme for the white ethnic population
- the estimated risk of notified TB in the white ethnic group if the school's BCG vaccination scheme were discontinued.

The evidence is presented in Table 36.

Table 36: Summary of evidence: vaccination and longitudinal trends in TB among children of school-going age

BCG use and longitudinal trend	Results Vaccinated *vs.* unvaccinated groups/BCG discontinued *vs.* continued	Statistical significance	Ref and NICE grade
Progressive decrease in protective efficacy in successive five-year follow-up periods	0.40, 0.33, 0.10, 0.09 *vs.* 2.50, 1.06, 0.26, 0.08 per 1000	p=0.01	{285} 1+

Annual decrease in TB notification rates in three cohorts covering a 29-year period	Ages 15–19: 5% *vs.* 10%	Not reported	{292} 2+
	Ages 20–24: 7% *vs.* 11%		
Estimated risk of notified TB between ages 15 and 30 in white UK-born people eligible for BCG schools programme	1984: 1/6,500 (BCG administered at age 13) *vs.* 1/700 (Mantoux test negative)	Not reported	{293} 2+
	1994: 1/17,000 (BCG administered at age 13) *vs.* 1/4,300 (Mantoux test negative)		
Estimated TB notifications prevented by BCG vaccination in the white school-aged population	1983: 557 at ages 15–29 due to 7.65 million vaccinations in previous 15 years	Not reported	{293} 2+
	1988: 370 at ages 15–29 due to 7.65 million vaccinations in previous 15 years		
Additional TB notifications due to discontinuing BCG schools vaccination in the white ethnic population	Discontinuation in 1986: 129 in 2,003 (ages 15–29)[15]	Not reported	{293} 2+
	Discontinuation in 1996: 51 in 2,013 (ages 15–29)		
Estimated risk of notified TB in the white ethnic population if BCG schools vaccination were discontinued	Discontinuation in 1986: 1/2,200 between ages 15 and 30 (first wholly unvaccinated five-year cohort aged 13 in 1987–91) *vs.* 1/2,700	Not reported	{293} 2+
	Discontinuation in 1996: 1/5,400 between ages 15 and 30 (five-year cohort aged 13 in 1997–2001) *vs.* 1/6,900		

[15] *Some of these would be secondary additional notifications outside the age group 15–29 years of age.*

8.3.52 Health economics

A decision analytic model was used to estimate the cost-effectiveness of the current school BCG programme. The model distinguished between a 'high-risk' group of children who should have already been offered BCG before the school programme (through neonatal or new entrant schemes) and a 'low-risk' group, which is the remainder of the 10–14-year-old cohort. The school BCG programme is potentially beneficial for low-risk children and as a catch-up for previously unvaccinated high-risk children. The model relies on the assumption that there is negligible transmission between the high-risk and low-risk groups.{294}

The model is a simple decision tree that estimates the number of primary cases for a cohort of 10–14-year-olds, the consequent number of secondary cases in the population, and the associated costs and health outcomes, with and without a school BCG programme. The effectiveness of school BCG for the low-risk group and the number of secondary cases per primary case were taken from Saeed et al (2002),{295} updating the work of Sutherland and Springett in 1989.{293} The benefits for unvaccinated high-risk children were then estimated. It is important to note that this method can only give approximate results for an infectious disease such as TB. A population dynamic model would be expected to provide more reliable results.

Whenever possible, the input parameters and assumptions for the model were based on best available empirical evidence. However, we could not find evidence to inform all of the important parameters. In such cases, estimates are based on judgement by the guideline economist and the GDG. There is some uncertainty over the results of the model due to

uncertainty over some of the input parameters for the analysis. In particular, the results are sensitive to the proportion of 10–14-year-olds in 'high-risk' groups, the estimated QALY loss due to TB, and the estimated cost of treating a case of TB.

Cost-effectiveness of school BCG for the low-risk group

The economic model suggests that the schools programme is not cost-effective for the low-risk group alone – with 0% in the high-risk group, the incremental cost per QALY gained (incremental cost-effectiveness ratio, ICER) is over £150,000 if we assume 15-year protection from BCG, and over £750,000 if we assume only 10-year protection. School BCG appears to be cost-effective for the 'low-risk' population only if their 10–15-year risk is very high: approximately 0.13–0.15%. This compares with current estimates of 0.03% (age 15–24) or 0.05% (age 15–29) (see Table 37).

Table 37: Cost-effectivensss of school BCG for low-risk group only by baseline risk of TB

Risk of TB over period of BCG protection (%)	10-year protection			15-year protection		
	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QALY)
0.03	718	1	767,800	720	1	696,100
0.05	671	3	193,500	674	4	185,300
0.07	625	6	104,100	629	6	100,700
0.09	578	9	67,700	583	9	65,900
0.11	532	11	48,000	538	11	46,900
0.13	485	14	35,700	492	14	35,000
0.15	439	16	27,200	447	17	26,800
0.17	392	19	21,000	401	19	20,800
0.19	346	21	16,300	355	22	16,300

Cost-effectiveness of school BCG as a catch-up for unvaccinated high-risk children

Based on the assumptions that 64% of high-risk children have been previously vaccinated, that they have a relative risk of 40 (compared with the low-risk group), and that BCG offers protection for 10 years, the schools programme appears to be cost-effective for areas with around 25–30% or more children in the high-risk group. If we assume 15-year BCG protection, school BCG appears cost-effective with around 10–15% or more in the high-risk group (see Table 38).

Table 38: Cost-effectiveness of school BCG by percentage of cohort in high-risk group

'High-risk' as % of cohort	10-year protection			15-year protection		
	Additional cost (£K)	QALYs gained	ICER (£/QALY)	Additional cost (£K)	QALYs gained	ICER (£/QALY)
0	718	1	767,800	674	4	185,300
5	646	4	180,700	573	8	70,800
10	574	6	92,400	471	13	37,600
15	502	9	56,700	370	17	21,700
20	430	11	37,400	268	21	12,500
25	358	14	25,300	167	26	6,400
30	286	17	17,100	65	30	2,200

These results are sensitive to the estimated mean cost of treatment and QALY loss per case of TB age 15–24/29.

8.3.6 From evidence to recommendations

The GDG noted that the schools BCG programme was for those at low risk of TB and previously unvaccinated, whilst those at higher risk of TB (see section 10.2) receive BCG vaccination either at birth or on entry to the UK.

Whilst BCG in school-age children has a protective efficacy of 75–80% lasting 10–15 years, the incidence of active TB in those at low risk is now in the order of 1 case per 100,000, with a continuing downward trend.

England and Wales meet the accepted international criteria for the cessation of universal BCG vaccination in a low-prevalence country,{291} and have done so at least since 2000.

Economic modelling shows that the schools programme is not cost effective, and extremely expensive with an incremental cost-effectiveness ratio between £696,000 and £767,000 for low-risk individuals.

The schools programme becomes cost-effective only if 15% or more of the children included are at higher risk and previously unvaccinated.

For these reasons, it was felt that routine BCG vaccination of children aged 10 to 15 in schools should not continue. Those children at risk will either have been vaccinated neonatally (see section 11.2) or on entry to the UK (see section 11.4). Where universal childhood screening and vaccination is thought appropriate for an area because of very high local incidence, then this would be better achieved by a local universal neonatal BCG policy.

8.3.7 Recommendations

134. Routine BCG vaccination is not recommended for children aged 10–14 years.

- Healthcare professionals should opportunistically identify unvaccinated children older than 4 weeks and younger than 16 years at increased risk of TB who would have qualified for neonatal BCG and provide Mantoux testing and BCG vaccination (if Mantoux negative).
- This opportunistic vaccination should be in line with the Green Book. **[2006, amended 2015]**

135. Mantoux testing should not be done routinely before BCG vaccination in children younger than 6 years unless they have a history of residence or prolonged stay (more than 1 month) in a country with a high incidence of TB. [2006]

8.4 BCG vaccination - For new entrants from high-incidence countries [2011]

8.4.1 Clinical introduction

The incidence of tuberculosis in new entrants from countries of high incidence (40/100,000 per year or greater) is high, peaking 2–3 years after first entry, and falling significantly after 10 years, but remaining well above general UK population rates (see Appendix K). Up to 30% of such recent arrivals from the Indian subcontinent are tuberculin negative.{296},{297} Since they will be living in communities with a rate of TB some 25 times that of the white UK-born community, they may benefit from BCG vaccination to reduce the risk of acquiring TB disease. Such a BCG policy would however have to take into account the possibility of false negative Mantoux test from HIV co-infection.

8.4.2 Current practice

In the Department of Health's Immunisation against infectious diseases (the Green Book) 1996,{3} the following recommendation is made for new entrants from countries with a high prevalence of tuberculosis, their children and infants wherever born.

'New entrants to the UK, including students, from countries with a high prevalence of tuberculosis, and all refugees and asylum seekers, should be tuberculin tested as part of the initial screening procedure unless there is definite evidence of a BCG scar. Those with positive reactions should be referred for investigation as they may require chemoprophylaxis or treatment. BCG immunisation should be offered immediately to those who are tuberculin negative.'

Under section 32.4.1d of the same document HIV-positive individuals are listed as one of the contraindicated groups to whom BCG vaccine should not be given with the following comment:

'BCG is absolutely contraindicated in symptomatic HIV positive individuals. In countries such as the UK where the risk of tuberculosis is low, it is recommended that BCG is withheld from all subjects known or suspected to be HIV positive, including infants born to HIV positive mothers. There is no need to screen mothers for HIV before giving BCG as part of a selective neonatal immunisation programme (see 32.3.2(e))'.

The newly updated chapter of the draft 2006 Green Book{21} states:

'BCG immunisation should be offered to... previously unvaccinated, tuberculin-negative new entrants under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater.'

Readers should also be aware of the recommendations made for neonates (see section 11.2).

8.4.3 Methodological introduction

Studies investigating the effectiveness of BCG vaccination in new entrants from high-risk countries in preventing TB infection or disease were targeted. No systematic reviews, randomised controlled trials, cohort or case control studies were found that directly addressed the area.

One meta-analysis conducted in the USA{298} demonstrated that BCG vaccine had protective efficacy across a wide range of study conditions, BCG strains, populations, age ranges and vaccine preparation methods. BCG efficacy in new entrants from countries with a high TB incidence was not addressed.

Since the meta-analysis did not use cross-design analysis, it was appropriate to grade evidence statements according to whether they were derived from the RCT (level 1), clinically controlled trial (level 2) or case control study (level 2) results.

Factors for consideration raised by the meta-analysis included:

- differences in the characteristics and methodological quality of individual studies were addressed by a sensitivity analysis, expressed as a study quality validity score
- among 13 prospective trials, study validity explained 30% of the between-study variance in the trials, and geographical latitude accounted for 41% of the variance
- among the 10 case-control studies, data validity score was the only variable to explain a substantial amount (36%) of the heterogeneity
- different strains of BCG were not associated with more or less favourable results in the 13 trials, as differing BCG strains administered in the same populations provided similar levels of protection.

One non-analytic study from the UK{299} was excluded due to methodological limitations presented in Appendix K.

8.4.43 Evidence statements

Evidence was found for the efficacy of BCG vaccination in preventing:

- pulmonary TB disease
- TB deaths
- TB meningitis
- disseminated TB.

Evidence for these four outcomes is presented in Table 39.

Table 39: Summary of evidence: BCG vaccination for new entrants

Outcomes	Intervention: BCG vaccinated *vs.* unvaccinated infants	Results	Association/statistical significance	Ref and NICE grade
Pulmonary TB disease	Seven RCTs	Protective effect 0.63	Combined RR 0.37 (95% CI 0.18 to 0.74)	{298} 1+
	Six clinically controlled trials	Protective effect 0.51	Combined RR 0.49 (95% CI 0.34 to 0.70)	{298} 2+
	Ten case control studies	Protective effect 0.50	Combined OR 0.50 (95% CI 0.39 to 0.64)	{298} 2+
TB deaths	Three RCTs and four clinically controlled trials	Protective effect 0.71	Combined RR 0.29 (95% CI 0.16 to 0.53)	{298} 2+
TB meningitis	Five case control studies	Protective effect 0.64 (based on 181 cases of TB meningitis)	Combined OR 0.36 (95% CI 0.18 to 0.70)	{298} 2+
Disseminated TB	Three case control studies	Protective effect 0.78	Combined OR 0.22 (95% CI 0.12 to 0.42)	{298} 2+

8.4.51 From evidence to recommendations

The GDG noted that there was little data in this field. The high rates of tuberculosis in recently arrived new immigrants from high incidence countries was also noted from epidemiological data over the last 25 years.

Although there is no direct evidence in this group in the UK, the meta-analysis cited above was regarded as applicable.

Analysis of the evidence on BCG efficacy has shown no evidence for persons aged over 35. The GDG felt that for this pragmatic reason, BCG vaccination should be limited to those under 36, unless they have occupational risk factors.

8.4.6 Recommendations

136. Offer BCG vaccination to new entrants[jj] who are Mantoux-negative who:

- are from high-incidence countries, and
- are previously unvaccinated (that is, without adequate documentation or a BCG scar), and
- are aged:
  - younger than 16 years, or
  - 16–35 years[kk] from sub-Saharan Africa or a country with a TB incidence of 500 per 100,000 or more. **[2006]**

8.5 BCG vaccination - For healthcare workers [2011]

8.5.1 Clinical introduction

Although earlier studies had not shown an association, in the 1990s healthcare workers were shown to have twice the expected incidence of TB, allowing for age, sex and ethnic factors.{300} Because of the risk of exposure, it became standard practice to recommend BCG vaccination to people commencing healthcare work who would have contact with patients or clinical material, if they had not had prior BCG vaccination, and were Mantoux test negative.

8.5.2 Current practice

In Immunisation against infectious disease (the Green Book),{3} the Department of Health recommended BCG vaccination for all those at higher risk of tuberculosis. Under section 32.3.2a this included:

'Health service staff who may have contact with infectious patients or their specimens. These comprise doctors, nurses, physiotherapists, radiographers, occupational therapists, technical staff in microbiology and pathology departments including attendants in autopsy rooms, students in all these disciplines, and any others considered to be at high risk. It is particularly important to test and immunise staff working within maternity and paediatric departments, and departments in which patients are likely to be immunocompromised, eg transplant, oncology and HIV units.'

The newly updated chapter of the draft 2006 'Green book'{21} states:

'People in the following occupational groups are more likely than the general population to come into contact with someone with TB:

- healthcare workers who will have contact with patients or clinical materials
- laboratory staff who will have contact with patients, clinical materials or derived isolates.'

8.5.3 Methodological introduction

Studies investigating the efficacy of BCG vaccination in health care workers for preventing the development of TB infection or disease in comparison to unvaccinated healthcare workers were targeted. One systematic review was found that addressed the topic.

[jj] People who have recently arrived in or returned to the UK from high-incidence countries.

[kk] The Green Book recommends BCG for new entrants only up to the age of 16 years. However, in this guideline BCG is recommended for those up to 35 years who come from the countries with the very highest rates of TB because there is some evidence of cost effectiveness.

One systematic review conducted in the USA{301} included two randomised controlled trials, two prospective cohort studies, one historically controlled study, one retrospective cohort study and six non-analytic studies. Information on the study methods and results was reported for only four of the six non-analytic studies. The scope was international, but all 12 studies were conducted in the northern hemisphere, 10 in temperate zones situated far from the equator, the eleventh in California, and for the twelfth, the specific setting was unknown.

The systematic review was methodologically sound, and hence it could technically be given a grading of 1+. However, the review did not conduct a meta-analysis due to the heterogeneity of study designs and methodological limitations in each of the studies. The methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements for this area. The review authors noted that despite methodological limitations, all six controlled studies reported a protective effect for BCG vaccination.

8.5.4 From evidence to recommendations

Whilst the systematic review was sound, all of the studies had multiple methodological flaws. There was however a consistent trend to benefit in the six controlled studies. Also, given the weight of evidence for the efficacy of BCG in other settings, it seemed unlikely that BCG would not be effective in this population. The GDG also noted that potential TB exposure continues throughout a career in individuals with patient or clinical material contact, and is not age limited.

There is not sufficient age-specific evidence to make recommendations on BCG vaccination for people over 35 but vaccination is recommended for healthcare workers of all ages because of the increased risk to them – and consequently the patients they care for – if they remain unvaccinated.

8.5.5 Recommendations

137. Offer BCG vaccination to healthcare workers and other NHS employees who have contact with patients or clinical specimens, irrespective of age, who:

- are previously unvaccinated (that is, without adequate documentation or a BCG scar), and
- are Mantoux (or interferon-gamma release assay) negative. **[2006, amended 2015]**

8.6 BCG vaccination for contacts of people with active tuberculosis [2011]

8.6.1 Clinical introduction

Contacts of cases of pulmonary tuberculosis are at risk of contracting TB. This is particularly the case with household or close contacts of sputum smear-positive disease, where up to 10% become infected (see section 12.2). It may take several weeks to develop an immune response to infection, as judged by a positive tuberculin skin test. A second Mantoux test has to be performed in those whose initial test is negative, six weeks after the initial negative one and a decision made with the second result.{6} Those with serial negative skin tests are deemed not to have been infected, but BCG vaccination up to and including the age of 35 years is recommended. The index case should be rendered non-infectious within a few weeks by anti-tuberculosis drug treatment, but tuberculin-negative contacts remain at risk if there are secondary cases.

8.6.2 Current practice

The Department of Health's Immunisation against infectious disease (the Green Book) 1996{3} recommended BCG vaccination for all those at higher risk of tuberculosis.{3} Under section 32.2d this included:

'Contacts of cases known to be suffering from active pulmonary tuberculosis. Contacts of a sputum smear positive index case may have a negative tuberculin skin test when first seen but be in the early stages of infection before tuberculin sensitivity has developed. A further skin test should be performed six weeks later and immunisation only carried out if this second test is negative. (If the second skin test is positive, the patient has converted and must be referred for consideration of chemoprophylaxis). However, if for some reason a further test is impossible, vaccine may be given after the first test. Newly born babies should be given prophylactic isoniazid chemotherapy and tuberculin tested after three to six months. If the skin test is positive, chemoprophylaxis is continued; if negative, BCG vaccine is given provided the infant is no longer in contact with infectious tuberculosis. Newly born contacts of other cases should be immunised immediately.'

The newly updated chapter of the draft 2006 Green Book{21} states:

'BCG immunisation should be offered to... previously unvaccinated tuberculin-negative contacts of cases of respiratory TB (following recommended contact management advice – currently Joint Tuberculosis Committee of the British Thoracic Society 2000 [{6}] and National Institute for Health and Clinical Excellence 2006 [this document]..'

8.6.3 Methodological introduction

The focus was on studies investigating the efficacy of BCG vaccination in contacts of those with diagnosed active tuberculosis disease in comparison to unvaccinated contacts from the same population. One cohort study and five non-analytic studies were identified. All studies addressed BCG vaccination of contacts prior to their exposure to the index case.

One prospective cohort study conducted in South Korea{302} over a period of approximately two and a half years reported on the protective efficacy of BCG vaccination against TB disease in child contacts. Four studies{278},{303},{304},{305} reported contact tracing results that included stratification of contacts by BCG vaccination status. BCG vaccination status was not the primary variable used to generate group allocation or to stratify the analysis of the results, and for this reason the studies were classified as non-analytic. One study was conducted in the UK (England, Wales and Scotland) and two studies in Scotland. A fourth study conducted in Brazil dealt with contacts of index cases diagnosed with MDR TB. Although the latitude effect could have influenced the study findings, the study was included since it focused on BCG vaccination in a contact population at risk of acquiring MDR TB disease. MDR TB is not addressed in the three UK-based studies.

A fifth non-analytic study was excluded due to methodological limitations, which are presented in the appendix K.

8.6.4 Evidence statements

Evidence on the efficacy of BCG vaccination in preventing TB disease was found for contacts:

- of index cases
- of index cases diagnosed with MDR TB
- belonging to different ethnic groups

The evidence is presented in Table 40.

Table 40: Summary of evidence: BCG vaccination for contacts of people with TB

Population	Results N (%) TB disease cases in BCG- vaccinated versus unvaccinated persons	Association/statistical significance	Ref and NICE grade
Contacts of index cases	Child contacts aged 0–5: protective effect 0.70; 46/806 (5.7) *vs.* 80/417 (19.2) scored six or higher, indicating TB disease	Not reported	{302} 2+
	Stratification by age: protective effect 0.74	Summary RR 0.26 (95%CI 0.62 to 0.82)	{302} 2+
	Close contacts: 14/1081 (1.3) *vs*. 149/3587 (4.2)	Not reported	{278} 3+
	Contacts: 16/1821 (0.88) *vs.* 62/3595 (1.72)	Not reported	{303},{304} 3+
	Contacts with new TB (active TB disease plus those on treatment for latent TB infection): protective effect 0.62; (1.15) *vs.* (3.06)	p<0.001	{303},{304} 3+
	Contacts: 14/1605 (0.87) *vs*. 34/1761 (1.93)	Not reported	{303},{304} 3+
	Contacts received chemotherapy/treatment for latent TB infection for TB disease/infection: protective effect 0.59; 23/1605 (1.4) *vs.* 60/1761 (3.4)	Not reported	{303},{304} 3+
Contacts of index cases diagnosed with MDR TB	Protective effect 0.69 (excluding three contact TB cases with drug-susceptible isolates); 8/153 (5) *vs.* 9/65 (14)	RR 0.35 (95%CI 0.13 to 0.99, p< 0.05)	{305} 3+
	TB disease found significantly more in unvaccinated MDR TB contacts	RR 3.1 (95%CI 1.2 to 8.1)	{305} 3+
Contacts belonging to different ethnic groups	Asian contacts: 7/425 (1.6) *vs.* 57/1479 (3.9)	Not reported	{278} 3+
	Non-Asian (mainly white) contacts: 7/656 (1.1) *vs.* 92/2108 (4.4)	Not reported	{278} 3+
	Asian contacts: 0/86 *vs.* 5/228 (2.19)	Not reported	{303},{304} 3+
	Non-Asian (mainly white) contacts: 16/1735 (0.92) *vs.* 57/3367 (1.69)	Not reported	{303},{304} 3+
	Incidence of TB in Black African *vs.* white contacts: 2.2 versus 0.4 per 1,000 person-years	p<0.001[21]	{305} 3+

21 Using Cox's regression test, ethnicity was no longer associated with incidence of TB disease.

8.6.54 From evidence to recommendations

The appraised evidence shows some protective efficacy for BCG vaccination given before contact with tuberculosis, but none of the studies addressed the efficacy of BCG

administered to tuberculin-negative contacts after exposure to TB. However, such individuals may be at increased risk from secondary TB cases if not vaccinated. As for new entrants, the potential benefit of BCG vaccination is reduced with age, and there is no reason to change the upper age limit of 35 years, which is currently widely used.

8.6.6 Recommendations

138. Offer BCG vaccination to Mantoux-negative contacts of people with pulmonary TB (see section 1.6.1 for details of contact tracing) if they have not been vaccinated previously (that is, there is no adequate documentation or a BCG scar) and are:

- aged 35 years or younger, or
- aged 36 years and older and a healthcare or laboratory worker who has contact with patients or clinical materials. **[2006, amended 2015]**

8.7 BCG vaccination - Other groups [2011]

The Department of Health currently recommends BCG vaccination for a range of other people who may be at risk from TB.{21} This guideline concentrated on the groups given individually above but for completeness this section addresses the other groups at risk, who stand to benefit from BCG vaccination. For veterinary surgeons, abattoir workers and other people working with animals, there are a number of possible sources of infection, but no standard occupational health screening. Workplace screening is likely to be provided by private sector firms, and is therefore outside the remit of NICE. However, a number of regulations apply:

- the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995, which require employers to notify the Health and Safety Executive
- the Management of Health and Safety at Work Regulations 1999, which require general standards of risk assessment
- the Control of Substances Hazardous to Health Regulations 2002, which require employers to assess infection risk and prevent or control exposure.

8.7.1 Recommendations

139. Offer BCG vaccination to previously unvaccinated, Mantoux-negative people aged 35 years or younger in the following groups at increased risk of exposure to TB, in accordance with the Green Book:

- veterinary and other staff such as abattoir workers who handle animal species known to be susceptible to TB, such as simians
- prison staff working directly with prisoners
- staff of care homes for older people
- staff of hostels for people who are homeless and facilities accommodating refugees and asylum seekers
- people going to live or work with local people for more than 1 month in a high-incidence country. **[2006]**

8.8 Strategies to increase uptake of BCG vaccination [2015]

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8.8.1 Clinical introduction

Measures to increase uptake of BCG vaccination, which is a primary prevention intervention aimed at sub-optimal uptake of vaccination by those eligible is an important activity in controlling and reducing TB infection rates. Sub-optimal uptake can lead to increased morbidity and mortality as a result from increased disease manifestation of tuberculosis.

Current UK guidance on vaccination for tuberculosis (TB) recommends that Bacillus Calmette-Guérin (BCG) vaccine should be offered to the following groups:

- infants living in high-prevalence areas of the UK (annual incidence >40/100,000);
- infants and children up to 16 years with a parent or grandparent born in a high-prevalence country;
- children up to 16 years who are contacts of cases of pulmonary TB;
- children up to 16 years who were born in or have lived for at least three months in a high-prevalence country;
- new entrants ages 16-35 from sub-Saharan Africa or countries with an incidence of > 500 per 100,000 and contacts ≤ 35 years
- healthcare workers and laboratory staff who will have contact with TB patients or clinical materials from TB patients;
- veterinary and staff such as abattoir workers who handle animal species known to be susceptible to TB, e.g. simians;
- staff of prisons, care homes for the elderly, hostels for homeless people and facilities accommodating refugees and asylum seekers.

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This policy has been in place since 2005. Prior to that date, there was a universal programme of BCG vaccination for adolescents, in addition to selective vaccination for neonates and contacts of TB cases along similar lines to the post-2005 policy.

8.8.2 Review questions

What is the effectiveness and cost effectiveness of strategies to increase the uptake of BCG vaccination among people at increased risk of developing active or latent TB.

What is known from systematic reviews about the effectiveness and cost-effectiveness of interventions to improve the uptake of vaccinations?

8.8.3 Evidence review

8.8.3.1 Literature review

The reviews for these questions were developed externally, by the London School of Hygiene and Tropical Medicine.

For each review question, a separate search strategy was developed utilising a number of different databases (please see each individual review for details of the search strategy, the databases searched, and inclusion and exclusion criteria). The evidence from the included studies relating to each review question has been critically appraised and quality ratings assigned according to the Centre for Public Health Methods Manual 2012 (3rd Edition). The full evidence tables all evidence statements and quality rating summaries for each review can be found in appendix G1-3 and summarised below.

The reviews include all evidence statements derived from the included studies, the evidence statement section below has extracted only those evidence statements that underpin the BCG uptake recommendations made by the committee.

This review focused on interventions aiming to increase the uptake of BCG vaccination among relevant groups. It aimed to synthesize evidence from outcome evaluation studies about the effectiveness of interventions to increase BCG uptake. It is supplemented by the review of reviews produced for the same phase of this project, which synthesizes review-level evidence on interventions to increase the uptake of vaccination in general (see Increasing the uptake of vaccinations: Review of Reviews) below).

For this review question, papers were identified from a range of databases (Applied Social Sciences Index and Abstracts (ASSIA), British Education Index (BEI), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Database of Systematic Reviews (CDSR), Cochrane Health Technology Assessment database (HTA), Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Science & Humanities, Embase EPPI Centre Trials Register of Promoting Health Interventions (TRoPHI), Education Resource Information Center (ERIC), Health Management Information Consortium (HMIC), MEDLINE in Process, MEDLINE, OpenGrey, Science Citation Index Expanded, Social Policy and Practice (SPP), Social Sciences Citation Index, Sociological Abstracts (SA) and non-database sources (NICE via www.nice.org.uk, Public Health Observatory via www.apho.org.uk, Public Health England via www.gov.uk/government/organisations/public-health-england).

Google was searched using a simplified version of the search string, and the advanced search options to limit to PDFs or word document files. The first 100 search results were scanned for relevance. The review team also searched PubMed using a time-limited search to identify any new items.

The searches were limited from 1993 to the most recent records (with the exception of the Conference Proceedings Citation Indexes, which were run from 2011 to the present).

In addition supplementary searching was undertaken to identify evidence, identified as relevant to the review using records selected for inclusion through the screening process in three ways:

- Forwards citation searching: Web of Science. All citations were added to Reference Manager
- BL Ethos (http://ethos.bl.uk/) to identify unpublished theses

The search strategy was designed to identify papers relating to outcome evaluations including but not limited to randomised, quasi-randomised and non-randomised control trials, cohort studies, case-control studies and case series were included where applicable to the criteria in the review.

Studies were excluded if:

- The population studied was not from a country which is a current OECD member
- The intervention was not an outcome evaluation and did not include either as a minimum pre- and post-test outcome data (or use random assignment to intervention and comparison groups).
- The outcome did not measure uptake of BCG.
- Interventions delivered by non-professionals without specific training in CM
- The study was not reported in English

From a database of 5372 unique abstracts, 164 full-text articles and reports were assessed for eligibility and 8 studies were included in the review. The critical appraisal tools (NICE, 2012) rate each study on a number of domains and gives an overall rating (high, medium or

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low) to each study on internal and external validity. With one exception, all studies received a low internal validity rating, largely due to poor reporting of methods, and the use of non-comparative designs. Five studies received medium external validity ratings (although this was interpreted liberally, to include any study providing more than minimal information about its context or population), two low and one high. See appendix G1 for detailed summaries of all critical appraisal results. For this review, of the 8 included studies 1 was rated high quality (++) and 7 low (–) quality.

8.8.3.2 Review of reviews

This review was conducted according to the methods guidance set out in the Methods for the development of NICE public health guidance (Third Edition). This review was designed to supplement the review of interventions to increase the uptake of BCG vaccination for TB (see section 8.8.3.1 above), and should be read in conjunction with this review. Guideline development on clinical and public health topics increasingly demands rapid access to the best available evidence to ensure evidence-informed decision making and practice. Rapid evidence assessments are literature reviews that use a variety of methods to accelerate or streamline traditional systematic review processes. In this instance, a brief systematic review methodology (Rapid Evidence Assessment), with limited database searching (on the basis that restricting to recent reviews allows indirect access to older primary data) was used. The focus was on any systematic review which reported data on the effectiveness and/or cost-effectiveness of interventions to improve the uptake of any vaccination in a high-income (OECD) country was included from the search results. While the review process was systematic throughout, and designed to minimize bias as far as possible, fully comprehensive searches were not conducted.

For this review question, papers were identified from a range of databases (Cochrane Libraray (CDSR, HTA and DARE), Embase via OVID, MEDLINE in Process via OVID, MEDLINE via OVID) and non-database sources (NICE via www.nice.org.uk, Public Health Observatory via www.apho.org.uk, Public Health England via www.gov.uk/government/organisations/public-health-england).

Google was searched using a simplified version of the search string, and the advanced search options to limit to PDFs or word document files. The first 100 search results were scanned for relevance.

The searches were limited from 2003 to the most recent records.

Studies were excluded if:

- The population studied was not from a country which is a current OECD member
- The outcome did not measure effectiveness and/or cost-effectiveness of interventions to improve the uptake of vaccination (descriptive data on rates of uptake, or determinants of uptake; data on the clinical effectiveness of vaccines themselves; data about views or beliefs regarding vaccination were all excluded)
- The study was not a systematic review (minimum inclusion criteria was that both search strategy and inclusion criteria were reported)
- The review did not include quality or critical appraisals of included studies
- The following were excluded: studies of vaccines used for immunotherapeutic treatment of disease; animal studies; studies of epidemiology or prevalence intended to inform vaccination programmes, but which do not report actual data regarding vaccination
- The study was not reported in English
- Published prior to 2003

From a database of 2334 unique abstracts, 215 full-text articles were assessed for eligibility and 27 studies were included in the review. The critical apprasial tools (NICE, 2012) provided

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an overall rating (high, medium or low) for each study. For this review of the 27 included studies 15 was rated high quality (++), 10 rated medium quality (+) and 2 low (–) quality.

8.8.43 Evidence statements

The first review (evidence statements marked 'a' below) covers primary studies on interventions to promote the uptake of BCG vaccination for tuberculosis. The second review (evidence statements marked 'b') covers review-level evidence on interventions to promote any vaccination. These first two are organised by intervention type. The third set of evidence statements (marked 'c') reflects the same evidence, but has been organised by population.

Staff training to increase BCG vaccination uptake [ES1a]

There is strong evidence from six studies (four UK[1-3,5] and two non-UK[4,6]) that interventions involving staff training may increase the uptake of BCG vaccination. One RCT[1] showed significantly higher uptake in the intervention group, with an odds ratio of 9.52 (95% CI 4.0–22.7). Five BA studies showed some increase in uptake[2-6](6% before to 88-90% after[3]; ~15% before to 88% after[4]; 11% before to 14% after[5]; 25.4% before to 25.8% after[6]), although in only two cases was statistical significance measured, and in neither of these did the increase reach significance[5,6]). The RCT1 involved training clinical staff to identify people eligible for BCG vaccination, computer-based reminders to staff, and financial incentives to primary care practices for carrying out TB screening. The BA studies[2-6] generally focused on staff training and did not use incentives.

Applicability: Most evidence is applicable to BCG vaccination in the UK. Four studies in this category (Athavale et al., 2006 (–); Gill and Scott, 1998 (–); Griffiths et al., 2007 (++); Tseng et al., 1997 (–)) were carried out in the UK, and one (Romanus, 2005 (–)) in Sweden, which has broadly similar patterns of TB infection and BCG policy to the UK. One study (Uskun et al., 2008 (–)) was carried out in Turkey, which has a policy of universal neonatal BCG vaccination, and may be less applicable, although it is worth noting high incidence areas in the UK have universal neonatal vaccination policies.

1 Griffiths et al., 2007 (++)

2 Athavale et al., 2006 (-)

3 Gill and Scott, 1998 (–)

4 Romanus, 2005 (–)

5 Tseng et al., 1997 (–)

Reminders to clinical staff to increase BCG vaccination uptake [ES2a]

One UK BA study[1] showed that computerised reminders to hospital staff can increase the uptake of BCG vaccination (18-24% before to 52-76% after). However, the data are difficult to interpret as the criteria for eligibility for BCG were defined differently at pre- and post-test.

Applicability: This evidence is directly applicable to BCG vaccination in the UK as the study was conducted in the UK.

1 Chappel and Fernandes, 1996 (–)

Contact tracing interventions to increase BCG vaccination uptake [ES3a]

There is inconclusive evidence from one UK BA study[1] as to whether revised contact tracing protocols can increase the uptake of BCG vaccination.

Applicability: This evidence is directly applicable to BCG vaccination in the UK as the study was conducted in the UK.

1 Ansari et al., 1998 (–)

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Reminders and recall to increase uptake of vaccinations [ES1b]

There is strong evidence from seven reviews[1-7] that recall and reminder interventions (general population 1.587 (1.14-1.75); children [*influenza*] 2.18 (1.29-3.70), [*routine vaccinations*] 1.47 (1.28-1.68); adults [influenza] 1.66(1.31-2.09), [*pneumococcus, tetanus, hep B*] 2.19(1.21-3.99) and adolescents 1.14 (0.98-1.31)[2]), including letters (*influenza and pneumococcus* 1.45 (1.30-1.61); 1.66(1.59-1.74) [4]), telephone calls (*influenza and pneumococcus* 2.74 (1.23-6.12); 2.86 (2.31-3.56)[4]); and text messages (*people travelling to high incidence countries* 1.19 (1.15-1.23)[1]), are effective in increasing the uptake of a range of vaccinations. Three meta-analytic reviews[2,3,5] show that these interventions have a medium to large effect size. There is evidence that these interventions are effective both for adults and older people (adults [*influenza*] 1.66(1.31-2.09), [*pnemoccoccus, tenatnus, hep B*] 2.19(1.21-3.99)[2] older people 1.21 (0.99-1.48) [*tailored*] ; 1.53 (1.33-1.76)[*generic*][5] 2.74 (1.23-6.12)[*telephone influenza*]; 2.86 (2.31-3.56)[*telephone pneumococcal*]; 1.45 (1.30-1.61)[*print materials influenza*] 1.66(1.59-1.74)[*print materials pneumococcal*][4]); and for parents of young children (2.18 (1.29-3.70), [*routine vaccinations*][2]). There is some suggestion from one review[6] that these interventions may be less effective in socio-economically disadvantaged populations.

Applicability: The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. There are no obvious limits to the applicability of this evidence, although the different context of healthcare service organisation may affect the delivery of interventions.

1 Free et al., 2013 (++)

2 Jacobson Vann and Szilagyi, 2009 (++)

3 Lau et al., 2012 (++)

4 Ndiaye et al., 2005 (++)

5 Thomas et al., 2010b (++)

6 Tuckerman et al., 2009 (++)

7 Williams et al., 2011 (++)

Patient education to increase uptake of vaccinations {ES2b]

There is mixed evidence from five reviews[1-5] on the effectiveness of patient education interventions (other than reminders) in promoting the uptake of vaccination including posters in waiting rooms (*influenza* 1.78 (0.53-6.01); *pneumococcus* 1.92 (1.09-3.40)[1]); brochures in offices (*influenza* 1.38 (0.82-2.33); *pneumococcus* 5.86 (3.29-10.44)[1]); . One review () finds community media campaigns to be effective (*influenza* 3.16 (1.35-7.37); *pneumococcus* 1.31 (1.28-1.55)[1], with medium to large effect size. The findings on health education for patients or parents of young children are mixed.

The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. This may limit the applicability of the findings, due to cultural or other differences.

1 Lau et al., 2012 (++)

2 Moxey et al., 2003 (–)

3 Ndiaye et al., 2005 (++)

4 Thomas et al., 2010b (++)

5 Tuckerman et al., 2009 (++)

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Incentives or disincentives for patients to increase uptake of vaccinations [ES3b]

There is mixed evidence from five reviews on the effectiveness of incentives or disincentives for promoting the uptake of vaccinations[1-5]. There is some evidence from two reviews that providing free vaccines is effective (1.98 (1.54-2.56)[2]; 5.43 (2.85-10.35)[4]). There is some evidence from two reviews (1.98 (1.54-2.56)[2]; 8.43 (3.95-18.0)[3]) suggesting that cash incentives may be effective. The evidence on conditional cash transfers[1] and penalties for welfare recipients [5] is inconclusive.

There are potential limits to the applicability of this evidence: for example the provision of free vaccines is of limited relevance to the UK context; the evidence on conditional cash transfers is from Mexico, a middle-income country; and the evidence on welfare penalties is from the USA, and may represent a different policy context.

1 Lagarde et al., 2009 (+);

2 Lau et al., 2012 (++);

3 Ndiaye et al., 2005 (++);

4 Thomas et al., 2010b (++);

5 Tuckerman et al., 2009 (++)

Home visiting and lay health worker interventions to increase uptake of vaccinations [ES4b]

There is strong evidence from four reviews [1-4] that home visiting and lay health worker interventions are effective in increasing the uptake of vaccination. Home visiting has been found to be effective for socio-economically disadvantaged parents[1,2,4] (1.19 (1.09-1.30)[1]; 1.23 (1.09-1.38)[2]; positive[4]) and for older people (1.30 (1.05-1.61)[3]), although effect sizes are small. However, there is evidence from three reviews[4,5,6] that home visiting interventions are ineffective for parents who use drugs or alcohol (0.67 (0.33-1.35)[5]; 1.09 (0.91-1.32)[6]), and mixed evidence from one review[7] for parents at risk for child abuse or neglect .

The majority of the evidence in these reviews appears to come from the USA, with few or no studies from the UK. There may be limits to the applicability of this evidence resulting from the different cultural, policy or demographic contexts.

1 Glenton et al., 2011 (++);

2 Lewin et al., 2010 (+);

3 Thomas et al., 2010b (++);

4 Tuckerman et al., 2009 (++)

5 Kaufman et al., 2013 (++)

6 Turnbull and Osborn, 2012 (++)

7 Selph et al., 2013 (+)

Community engagement to increase uptake of vaccinations [ES5b]

There is strong evidence from two reviews[1,2] ()that community engagement interventions, including outreach to at-risk groups and information or case management, are effective in increasing the uptake of vaccinations. These interventions appear to be effective for the general adult population (3.0 (1.28-7.03)[1]) and for disadvantaged parents (positive findings[2])

The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. There may be limits to the applicability of this evidence resulting from the different cultural, policy or demographic contexts.

1 Lau et al., 2012 (++);

2 Tuckerman et al., 2009 (++)

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Health checks and well-child clinics to increase uptake of vaccinations [ES6b]

There is mixed evidence from one review[1] on the effectiveness of routine health checks in increasing vaccination uptake. There is medium evidence from one review[2] (positive direction of effect) that well-child clinics, i.e. specialist preventive services for parents of young children, are effective in increasing vaccination uptake.

There is limited information on the country and context of the studies included in this category, and most appear to be in the USA. There may be limits to the applicability of this evidence to the UK resulting from the different contexts of health service delivery.

1 Boulware et al., 2006 (++)

2 Coker et al., 2013 (+)

School-based interventions to increase uptake of vaccinations [ES7b]

There is medium evidence from one review[1] (positive direction of effect) that policies requiring children to be vaccinated in order to attend school or day care is effective in increasing the uptake of childhood vaccinations. There is insufficient evidence on other school-based interventions.

The majority of the evidence in this review appears to come from the USA, with no evidence from the UK. There may be limits to the applicability of this evidence to the UK resulting from the different contexts in terms of educational policy.

1 Tuckerman et al., 2009 (++)

National vaccination programmes to increase uptake of vaccinations [ES8b]

There is medium evidence from one review[1] that national vaccination programmes, including policy changes and promotion and education campaigns, increase the uptake of childhood vaccinations.

The evidence in this review comes from Australia and Finland, with no evidence from the UK. There may be limits to the applicability of this evidence due to the different cultural or policy contexts.

1 Tuckerman et al., 2009 (++)

Reminders to clinicians to increase uptake of vaccinations [ES9b]

There is strong evidence from six reviews[1-6] (median +13.1% (IQR 12.2% to 20.7%)[1]; 4.69 (1.25-17.53)[2] ; 1.53 (1.26-18.5) [*influenza*] & 2.13 (1.50-3.03) [*pneumococcal*][3]; median +17.9%[4]; median +3.8% (IQR 0.5% to 6.6%)[5]; positive direction of effect[6]) that reminders to clinicians are effective in increasing vaccination uptake. However, two reviews report more mixed findings[7,8] . Two meta-analytic reviews[2,3] (4.69 (1.25-17.53)[2] ; 1.53 (1.26-18.5) [*influenza*] & 2.13 (1.50-3.03) [*pneumococcal*][3]) show medium to large effect sizes.

The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. There may be limits to the applicability of this evidence due to the different contexts of health service delivery.

1 Arditi et al., 2012 (+);

2 Holt et al., 2012 (++);

3 Lau et al., 2012 (++);

4 Ndiaye et al., 2005 (++);

5 Shojania et al., 2011 (++);

6 Tuckerman et al., 2009 (++)

7 Souza et al., 2011 (++);

8 Thomas et al., 2010b (++)

Incentives and bonus payments to providers to increase uptake of vaccinations [Es10b]

There is medium evidence from six reviews[1-6] that incentives and bonus payments to clinicians or practices, such as pay-for-performance schemes or payments per vaccination carried out, is likely to increase vaccination uptake. Two meta-analytic reviews[3,5] (1.52 (1.20-1.93) [*influenza*] and 7.43 (2.25-24.53)[*pnemococcal*][3]; 2.22 (1.77-2.77)[*older people*][5]) find medium to large effect sizes.

The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. There may be limits to the applicability of this evidence to the UK resulting from the different policy contexts and healthcare funding systems.

1 Eijkenaar et al., 2013 (–);

2 Houle et al., 2012 (+);

3 Lau et al., 2012 (++);

4 Scott et al., 2011 (+);

5 Thomas et al., 2010b (++);

6 Tuckerman et al., 2009 (++)

Clinician education to increase uptake of vaccinations [ES11b]

There is mixed evidence from five reviews[1-5] () regarding clinician education programmes to promote vaccination. Two reviews indicate that clinician education does not have a significant effect[2,5] (), one indicates that it is effective ([infants] positive direction of effect[4]), and one shows mixed findings ([influenza] 0.99(0.94-1.04) and [pneumococcal] 1.54 (1.19-1.99)[1]). One review (positive direction of effect[3]) indicates that facilitators working with clinical practices may be effective in increasing vaccination uptake.

The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. There are no obvious limits to the applicability of this evidence.

1 Lau et al., 2012 (++);

2 Ndiaye et al., 2005 (++);

3 Thomas et al., 2010b (++);

4 Tuckerman et al., 2009 (++);

5 Williams et al., 2011 (++)

Audit and feedback to increase uptake of vaccinations [ES12b]

There is mixed evidence from 5 reviews[1-5] (1.83 (1.28-2.61) [*influenza*] and 1.18 (0.57-2.45) [*pneumococcal*][1]; 3.43 (2.37-4.97) [feedback with benchmarking][3]; positive direction of effect[2,4] and mixed finding[5]);) regarding the effectiveness of clinical audit and feedback interventions on the uptake of vaccination. Two reviews suggest that these interventions are effective[2,4], while the findings of the other three are mixed (1.83 (1.28-2.61) [*influenza: audit and feedback*] versus, 0.99 (0.94-1.04) [*influenza: continuous improvement*][1] ;3.43 (2.37-4.97) [feedback with benchmarking] versus, 0.77 (0.72-0.81) [educational outreach and feedback][3]; mixed direction of effect[5]).

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The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. There may be limits to the applicability of this evidence resulting from the different contexts of clinical practice.

1 Lau et al., 2012 (++);

2 Ndiaye et al., 2005 (++);

3 Thomas et al., 2010b (++);

4 Tuckerman et al., 2009 (++);

5 Williams et al., 2011 (++)

Changes to service delivery models to increase uptake of vaccinations [ES13b]

There is strong evidence from three reviews [1-3] that a range of changes to service delivery are effective in increasing vaccination uptake. One review (1.32 (1.14-1.52) [*influenza*] and 1.66 (1.59-1.74) [*pnemococcal*][1]) shows that delivering vaccination services in alternative sites (such as patients' homes or worksites or community pharmacies), and changing the team involved in delivering services (e.g. training nurses to give vaccinations) are both effective, with medium to large effect sizes. One review shows that group visits for people with chronic diseases are effective (2.44 (1.42-4.20) [*influenza*] and 2.25 (1.30-3.92) [*pneumococcal*] [1]). One review finds mixed evidence for case management (1.66 (0.81-3.43) [*influenza*] and 1.49 (1.05-2.13) [*pneumococcal*][1]). One review shows that increasing clinic accessibility (e.g. extended opening hours) in conjunction with education or reminders is effective[2]. One review finds that opportunistic vaccination policies are effective in hospitals and prisons, but not in GP services[3]. The findings on hospital vaccination policies are mixed ((mixed direction)[2]; (positive findings)[3]).

The majority of the evidence in these reviews appears to come from the USA, with only a small amount of evidence from the UK. There may be limits to the applicability of this evidence resulting from the different health system or demographic contexts.

1 Lau et al., 2012 (++);

2 Ndiaye et al., 2005 (++);

3 Tuckerman et al., 2009 (++)

Programmes to increase uptake of vaccinations among healthcare workers [ES14b]

There is mixed evidence from five reviews[1-5] regarding the effectiveness of multi-component interventions, generally combining education and changes to vaccination service delivery, to increase the uptake of vaccination among healthcare workers. These reviews find that although most studies show some positive direction of effect, in most cases it does not attain significance (Mixed findings[1]; Positive findings[2]; Mixed findings (6/14 sig effective)[*education and access in hospitals*] & Positive findings (8/9 sig effective)[*education and access in other settings*][3]; positive findings[4]; positive findings[5]).

The evidence in these reviews appears to come from a range of countries, with relatively little evidence from the UK. There may be limits to the applicability of this evidence resulting from the differences in healthcare delivery and policy.

1 Burls et al., 2006 (+);

2 Jordan et al., 2004 (+);

3 Lam et al., 2010 (++);

4 Ndiaye et al., 2005 (++);

5 Thomas et al., 2010a (+)

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Increasing uptake of BCG vaccinations in neonates [ES1c]

There is weak but relatively consistent evidence from four before and after studies[1-4] that clinician training interventions may be effective in increasing the uptake of BCG among neonates ((6% before to 88-90% after[2]; ~15% before to 88% after[3]; 11% before to 14% after[4]) . There is weak evidence from one before and after study[5] that computer reminders to hospital staff may increase the uptake of BCG among neonates (18-24% before to 52-76% after[5]).

All but one study (Romanus 2005) in this category were conducted in the UK and targeted increases in neonatal vaccination uptake within the current policy context.[1]

1 Athavale et al., 2006 (–);

2 Gill and Scott, 1998 (–);

3 Romanus, 2005 (–);

4 Tseng et al., 1997 (–)

5 Chappel and Fernandes, 1996 (–)

Increasing uptake of BCG and other vaccinations in infants and children [ES2c]

There is evidence from one before and after study[1] that clinician training interventions are ineffective in increasing the uptake of BCG among infants (25.4% cover before to 25.8% cover after[1] and odds ratio of 9.52 (95% CI 4.0–22.7)[2]). There is strong evidence from one meta-analytical systematic review that reminders to parents are significantly associated in increasing the uptake of vaccinations for infants and children (OR 2.18 (1.29-3.70) [influenza] and OR 1.47 (1.28-1.68) [routine childhood vaccinations][3]),two non-meta-analytic reviews show somewhat more mixed findings[4,5] . There is mixed evidence regarding parent education to increase the uptake of vaccination for infants and children[4,5] . There is mixed and inconclusive evidence regarding welfare penalties in low income families[5] and conditional cash transfers for parents[6] to increase the uptake of vaccination for infants and children. There is strong evidence from three reviews that home visiting and lay health worker interventions targeted at disadvantaged or low-income families are effective in increasing the uptake of vaccinations for infants and children (RR 1.19 (1.09-1.30)[7]; RR 1.23 (1.09-1.38)[8]) however, there is evidence from three reviews that home visiting interventions are ineffective for parents who use drugs or alcohol[5,9,10] (RR 0.67 (0.33-1.35)[9] ; RR 1.09 (0.91-1.32)[10]), and mixed evidence from one review for parents at risk for child abuse or neglect[11]. There is medium evidence from one review that community outreach programmes are effective in increasing the uptake of vaccinations for infants and children[5] . There is medium evidence from one review that well-child clinics, i.e. specialist preventive services for parents of young children, are effective in increasing the uptake of vaccinations for infants and children[12]. There is medium evidence from one review that policies requiring children to be vaccinated in order to attend school or day care are effective in increasing the uptake of vaccinations for children[5] . There is medium evidence from one review that clinician education, and clinical audit and feedback, are effective in increasing the uptake of vaccinations for infants[5] .

The one primary study in this category was conducted in Turkey, which has a policy of universal BCG vaccination, and so may not be applicable to areas of the UK where a universal vaccination policy is not in place. The review-level evidence comes from a range of countries and context and there may be some limits to applicability to the UK context as a result of different healthcare systems.

1 Uskun et al., 2008 (-);

2 Griffiths et al., 2007 (++);

3 Jacobsen-Vann and Szilagyi., 2009 (++);

4 Tuckerman et al., 2009 (++);

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5 Williams et al., 2011 (++);

6 Lagarde et al., 2009 (+);

7 Glenton et al., 2011 (++);

8 Lewin et al., 2010 (+);

9 Kaufman et al., 2013 (++);

10 Turnbull and Osborn, 2012 (++)

11Selph et al., 2013 (+);

12Coker et al., 2013 (+)

Increasing uptake of BCG and other vaccinations in new entrants [ES3c]

There is strong evidence from one randomised control trial[1] that an intervention which involved training clinical staff to identify people eligible for BCG vaccination, computer-based reminders to staff, and financial incentives to primary care practices for carrying out TB screening, can increase the uptake of BCG vaccination(OR 9.52 (4.0–22.7)) in a population including a substantial proportion (around 14%) of immigrants .

This study was conducted in the UK.

1 Griffiths et al., 2007 (++)

Increasing uptake of BCG and other vaccinations in contacts of TB cases [ES4c]

There is inconclusive evidence from one BA study[1] as to whether revised contact tracing protocols can increase the uptake of BCG vaccination among contacts of TB cases.

This study was conducted in the UK.

1 Ansari et al., 1998 (–)

Increasing uptake of BCG and other vaccinations among healthcare workers [ES5c]

There is mixed evidence from five reviews[1-5] regarding the effectiveness of multi-component interventions, generally combining education and changes to vaccination service delivery, to increase the uptake of vaccination among healthcare workers. These reviews find that although most studies show some positive direction of effect (for example Mixed findings (6/14 sig eff) [education & access in hospitals] and Positive findings (8/9 sig eff) [education & access in other settings)[3], in most cases it does not attain significance[1,2,4,5].

The evidence in these reviews appears to come from a range of countries, with relatively little evidence from the UK. There may be limits to the applicability of this evidence resulting from the differences in healthcare delivery and policy.

1 Burls et al., 2006 (+);

2 Jordan et al., 2004 (+);

3 Lam et al., 2010 (++);

4 Ndiaye et al., 2005 (++);

5 Thomas et al., 2010a (+)

8.8.5 Evidence to recommendations

Relative value of different outcomes	As this chapter focused solely on increasing uptake of vaccinations, there is no relative value for different outcomes. Although the GDG found the review of reviews useful, they were keen to ensure that interventions and associated outcomes inform BCG specific studies were given more weight in discussion and influence than evidence from the review of reviews, largely because of

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	differences in target population groups from the broader literature.
Trade-off between benefits and harms	The BCG immunisation programme is a risk-based programme in the UK, the key part being a neonatal programme targeted at protecting those children most at risk of exposure to TB, particularly from the more serious childhood forms of the disease. The benefits of increasing uptake of BCG are that people under 16 classified as at high risk are protected from contracting TB with vaccination being found 70-80% effective against most severe forms of the disease such as TB meningitis in children following meta-analytical assessments (Rodrigues et al., 1993). There are few data on the protection afforded by BCG vaccine when it is given to adults (aged 16 years or over), and virtually no data for persons aged 35 years or over (Green book p.394, 2011) Further details regarding these benefits, contraindications and adverse reactions can be found in the Green Book: Chapter 32 'Tuberculosis' The BCG immunisation programme is a risk-based programme in the UK, the key part being a neonatal programme targeted at protecting those children most at risk of exposure to TB, particularly from the more serious childhood forms of the disease. There are however, a number of risks of increasing BCG uptake. There is a risk of disseminated BCG infection in patients with immunocompromise and also of severe local reactions in people with with septic skin conditions or eczema, those who have previously been vaccinated with BCG, or due to faulty injection technique (Green Book, 2011) There may also be a number of adverse reactions to BCG ranging from headache, fever or allergic reactions, although severe reactions are rare. There may also be serious adverse reactions including abscess or keloid scarring for which there are protocols for reviewing and recording these reactions (Green Book, 2011). The GDG noted that vaccinating neonates before discharge from hospital was the best case scenario, partly because some groups at increased risk may not have a stable permanent residence and if the family moves just after birth/hospital discharge the neonate may not be vaccinated in the community. However, the GDG was mindful that this must not result in discharge being delayed inappropriately. They also noted that if vaccination need and status are poorly communicated at the handover between maternity services and primary care, it may have an impact on the likelihood of the baby being vaccinated. The GDG discussed a number of groups for whom risk may be increased, but for whom there was no available evidence on increasing uptake; in particular contact tracing and people travelling to high incidence countries. This led to the recommendation to opportunistically identify eligible groups, along with the educational recommendations including incorporation of a case definition for at risk groups and links to the Green Book for a full list of groups and individuals eligible for BCG vaccination. In addition looked after children and young people were included as a group in whom to opportunistically identify eligibility due to committee experience of these children particularly when also new entrants being missed resulting in significant morbidity (miliary TB) and mortality. The GDG noted there may have been appropriate evidence on which to make recommendations for increasing uptake in healthcare workers available from the reviews. However, because occupational health is out of scope for the update work, the GDG did not make recommendations for this group. The GDG discussed call (that is, immunisations due) recall (immunisations overdue) reminder interventions, noting consistent evidence of their effectiveness. They recognised that some clinical systems may have limited capacity to deliver SMS or other types of reminders, as a result of technical limitations of the systems available within GP practices for example. However, the GDG felt it necessary to include all reminder types in the recommendation to ensure that the most effective and up to date options

	were presented as appropriate methods for the clinical community, and to reflect the interventions that should be aspired to in the UK. There was debate about the effectiveness of educational interventions alone as a result of the mixed findings in some of the BCG specific and broader vaccination studies from the review of reviews. The evidence from Griffiths et al, 2007 (+), was compelling, but this was a multi-component intervention that also included reminders and incentives. However, the GDG agreed that awareness raising is a core component of education, and that increasing the profile of TB risk and BCG eligibility is likely to have benefits not only for BCG uptake but possibly wider benefits by improving knowledge and awareness of TB signs and symptoms and the groups at particular risk potentially reducing diagnostic delay as well as improving identification of the groups eligible for BCG vaccination. Therefore, the GDG included education within the multi-component interventions recommended to increase BCG uptake. The needs of families who were disadvantaged were also discussed. ES1b indicated that call-recall interventions may be less effective in socio-economically disadvantaged groups, thus the need for community outreach or home visiting interventions in addition to reminder/call-recall interventions was determined to be warranted by the GDG in these groups despite the potential additional costs (ES4b and 5b). The reasoning behind this was that these groups of adults/parents were those who may be at higher risk of TB and thus, their children may be at increased risk of close contact with someone with active TB.
Trade-off between net health benefits and resource use	The GDG noted that no specific evidence for cost effectiveness of interventions aimed at increasing the uptake of BCG vaccination was identified. Despite this potential limitation, they noted that findings regarding the type of intervention shown to be effective and cost effective data from other NICE guidelines (NICE: Public Health Guidance 21 'Increasing Vaccination Uptake') were consistent. This consistency, along with the GDG's view that their expert consensus, experience and knowledge of these types of intervention were appropriate and relevant for extrapolation, means that the interventions recommended are likely to be cost effective. The committee discussed the importance of focussing on neonates for BCG vaccination as a primary prevention intervention and agreed that as it isd likely all wards now have computer/IT systems that have capacity to generate reminders and that it was a much greater risk for eligible babies to be discharged wihout vaccination particularly if they then went on to contract the disease (or to move away soon after birth, as some high risk groups are particularly mobile) they considered that the cost of implemeting this intervention would be very low given the possible benefits and did not require formal cost effectiveness evidence particularly as there were other additional benefits such as identifying high risk population groups for other interventions. There was additional discussion of incentivising GP practices. As above the evidence specific to BCG was from a multi-component RCT, which was supported by the evidence on incentives in other vaccination practices. However, there was some concern this may result in the need for a DES (directly enhanced service), with the potential for large costs to the healthcare sector. In addition it was also considered that this work should already be being completed under the childhood vaccination schedule (see here) for at risk groups; primary care already receives a tariff for this, so this could lead to double payment. However, it was also recognised that despite the tariff, vaccination rates in at risk groups remained low in particular areas where selective neonatal vaccination was the norm and given the evidence from the European paediatric network recently identifying BCG was better from a preventative perspective than previously thought it was worth consideraing incentivising practices. Furthermore, incentivising the practice may provide for improved capacity for offering BCG and encourage practices

	to take ownership of the issue particularly if staff training opportunity costs can be off-set. However, the GDG agreed to weaken the recommendation to allow local decision making based on vaccination rates and local needs assessments.
Quality of evidence	The GDG noted that the evidence base was broad (despite any gaps noted below) and the quality ranged from very low to high. While recognising the limitations in the quality of the evidence, the GDG agreed that their expert consensus and experience would be a substantive part of the evidence base for the development of the recommendations. Most studies were carried out in the UK, and hence these should be broadly applicable to current UK practice, although detailed information on populations and contexts was usually lacking. The studies reflect some local variability in which groups were considered eligible for BCG (and, again, less than completely clear reporting), although this is unlikely to be a major barrier to applicability. The main limitations of the BCG specific review relate to the quantity and quality of the primary evidence. As discussed in section 3.2 of review 1a in appendix G1, all the included studies except one received low quality ratings for internal validity. Several limitations are seen across the studies, relating particularly to study design (specifically the absence of control groups), the reporting of population characteristics and intervention content, and data analysis. In addition, one specific issue not reflected in the critical appraisal tools, and discussed in the full review is the confusion (and sometimes clear inconsistency) in how eligibility for BCG was evaluated and recorded. Since this affects the denominator of the fraction representing BCG coverage rates, it results in serious ambiguities in how the latter outcome variable should be interpreted in several studies. The GDG discussed the use of the review level material in depth and determined that it was appropriate. The GDG agreed that the evidence from the review level material not only supported the evidence found in the limited number of BCG specific papers but was also consistent with their own knowledge and experience of the kind of interventions being delivered. The GDG also considered whether evidence on the uptake of other types of vaccine could be extrapolated for BCG or whether different population groups (i.e. older people) and/or vaccination types (i.e. flu or pneumococcal) had the potential to affect the likelihood of uptake. The GDG agreed this was unlikely to be the case and that the review level material was valid for inclusion within the evidence base underpinning the recommendations. Further it was noted that the review of reviews had been developed, critically appraised and presented to the committee using the same methods and processes as the BCG specific review and corroborated the recommendations made in other NICE guidance (NICE: Public Health Guidance 21 ‘Increasing Vaccination Uptake), which they considered robust and appropriate to the topic. The majority of the evidence involved considered multi-component interventions (i.e. incentives, education and reminder systems) so it was difficult to distil out the effectiveness of individual sub-components. The GDG used the review of reviews to triangulate the evidence on individual sub-components where possible, and despite some weakness or inconsistency in the literature the overwhelming agreement was that all components are likely to play a role and should be delivered as a package, because ascertaining which elements provided greatest benefit for different population groups would be difficult without further research. In particular, the evidence on educational interventions from the review of reviews supported the incorporation of educational interventions despite some inconsistency in the findings of the BCG studies identified in the review.
Other considerations	There was some debate about the role school nurses play in improving BCG uptake, specifically in the delivery of the vaccination. However, the GDG was concerned that they had not received any specific evidence on this

	population group and the effectiveness of school nursing interventions to increase BCG uptake and that in particular, in low incidence areas nursing staff may not be able to maintain an appropriate level of practice experience. Therefore, despite some members of the GDG encouraging this as a useful and beneficial approach, the consensus was that they would not be included in the recommendations. The GDG noted and discussed the fact that different areas of the UK may have different policies in place (such as selective neonatal BCG vaccination in areas of low incidence and universal vaccination in areas of high incidence). It was thought this difference may make a large contribution to variability in vaccination rates because of lower awareness in low incidence areas. This is one of the reasons why the recommendations for training, practice incentives and computer reminder technology are directed at all areas irrespective of local incidence rates.

8.8.6 Recommendations

140. To improve the uptake of BCG vaccination, identify eligible groups (in line with the Department of Health's Green Book) opportunistically through several routes, for example:

- new registrations in primary care and with antenatal services
- people entering education, including university
- links with statutory and voluntary groups working with new entrants and looked-after children and young people
- during contact investigations. **[new 2015]**

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141. When BCG is being recommended, discuss the benefits and risks of vaccination or remaining unvaccinated with the person (or, if a child, with the parents), so that they can make an informed decision. Tailor this discussion to the person, use appropriate language, and take into account cultural sensitivities and stigma. [2006]

142. If people identified for BCG vaccination through occupational health, contact tracing or new entrant screening are also considered to be at increased risk of being HIV positive, offer them HIV testing before BCG vaccination[II]. [2006]

BCG vaccination in neonates (0–4 weeks)

143. Identify babies eligible for vaccination (in line with the Green Book) before birth, ideally through antenatal services. [new 2015]

144. Preferably vaccinate babies at increased risk of TB before discharge from hospital or before handover from midwifery to primary care. Otherwise, vaccinate as soon as possible afterwards, for example, at the 6-week postnatal check. [new 2015]

145. Incorporate computer reminders into maternity service (obstetrics) IT systems for staff, to identify and offer BCG vaccination to babies eligible for vaccination. [new 2015]

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[II] See the British HIV Association guideline for details of further action in HIV-positive patients.

146. Provide education and training for postnatal ward staff, midwives, health visitors and other clinicians on identifying babies eligible for vaccination, local service information and providing BCG vaccination, including:

- case definition for at-risk groups to be offered vaccination
- information about the local BCG vaccination policy that can be given verbally, in writing or in any other appropriate format (see sections 1.1.1 and 1.1.2) to parents and carers at the routine examination of the baby before discharge
- local service information about BCG vaccination, such as pre-discharge availability of neonatal vaccination, local BCG clinics and referral for BCG vaccination if this is not available in maternity services
- administration of BCG vaccination and contraindications. **[new 2015]**

Encouraging uptake among infants, older children and new entrants

147. Deliver the following interventions in primary care settings to improve uptake of BCG vaccination in people from eligible groups (as outlined in the Green Book):

- education and support for practice staff, including:
    - raising awareness of relevant guidelines and case definition for at-risk groups
    - promoting BCG and TB testing in eligible groups
- incorporating reminders for staff (prompts about eligibility for BCG) on practice computers (for example, embedded in medical records)
- consider financial incentives for practices for identifying eligible groups for BCG and TB testing
- reminders ('immunisations due') and recall ('immunisations overdue') for people who are eligible for vaccination or for parents of infants and children who are eligible, as outlined in the Green Book. (This could include written reminders, telephone calls from a member of staff or a computerised auto dialler, text messages or a combination of these approaches.) **[new 2015]**

148. If infants or older children are from disadvantaged families, also offer interventions that provide face-to-face information and advice on the importance of immunisation. These should be delivered by trained lay health workers, community-based healthcare staff or nurses, using community outreach and home visits. [new 2015]

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9 Adherence

9.1 'Identifying and managing tuberculosis among hard-to-reach groups' [PH37]

9.1.1 Introduction

This chapter briefly captures the evidence on which Public Health guideline 37 (PH37) 'Tuberculosis- hard-to-reach groups' was based. Some of the recommendations from this guideline have been incorporated into this updated guidance being consulted on in this section (others have been incorporated elsewhere in the guideline). The following five sub-headings provide a brief overview of the evidence on which NICE public health guideline 37 is based and that was reviewed by a committee the programme development group (PDG) using the Public Health process and methods to develop recommendations. These recommendations may have subsequently been adapted for inclusion into this guideline 'Tuberculosis-Update' NGXXX.

'Tuberculosis - hard-to-reach groups' (PH37) was developed to improve the way tuberculosis (TB) among hard-to-reach groups was identified and managed. It was for commissioners and providers of TB services and other statutory and voluntary organisations that work with hard-to-reach groups.

The main groups considered were:

- people who are homeless
- substance misusers
- prisoners
- vulnerable migrants

The recommendations covered:

- strategic oversight and commissioning of TB prevention and control activities
- raising and sustaining awareness of TB among health professionals and those working with hard-to-reach groups – and among the hard-to-reach groups themselves
- local needs assessment
- cohort review
- commissioning multidisciplinary TB support
- identifying and managing TB (including contact investigations)
- rapid-access TB services and enhanced case management
- the provision of accommodation during treatment.

9.1.2 Evidence Reviews (including Health Economic Reviews)

Four reviews were commissioned to inform the development of guidance on Tuberculosis – hard to reach groups.

The four evidence reviews are:

Review 1: 'Tuberculosis evidence review 1: Review of barriers and facilitators'

Review 2: 'Evidence review on the effectiveness and cost effectiveness of interventions aimed at identifying people with tuberculosis and/or raising awareness of tuberculosis among hard-to-reach groups'

Review 3: 'Evidence review on the effectiveness and cost effectiveness of interventions aimed at managing tuberculosis in hard-to-reach groups'

Review 4: 'Evidence review on the effectiveness and cost effectiveness of service models or structures to manage tuberculosis in hard-to-reach groups'

See appendix G8-11 for the full reviews including quality assessments and evidence tables for all included studies.

9.1.37 Economic Analysis

The economic analysis looked at the cost effectiveness of using mobile X-ray screening and enhanced case management – combined and separately – to identify and manage TB among homeless and prison populations. This was compared with current practice. The analysis also estimated the number of cases of pulmonary TB that would be averted due to earlier detection.

The results indicate that the interventions are most cost effective among populations with the highest prevalence of TB. Likewise, the benefit of ensuring treatment is completed is greater among those at high risk of transmitting TB (that is, among groups where TB prevalence is highest).

The recommendations for vulnerable migrants are largely based on existing NICE guidance (clinical guideline 117).

Estimates of cost per quality-adjusted life years (QALY) are presented for mobile X-ray screening. They are expressed as a threshold analysis (not as a cost per QALY) for enhanced case management and for mobile X-ray screening combined with enhanced case management. Sensitivity analyses were performed on key parameters, including prevalence of disease.

The economic analysis indicated how much it is worth spending to raise treatment completion rates from 55% to 75% among two separate populations: 10,000 homeless people and10,000 prisoners. It is based on the assumption that the NHS and other government bodies would be prepared to spend up to £20,000 to gain one QALY. The results suggest that it would be cost effective to spend an estimated £21,000 extra per additional case found among homeless people, when the prevalence of TB among this group is 778 cases per 100,000. For a prison population with a prevalence of 208 cases per 100,000, it would be cost effective to spend an additional £35,000 per additional case of active TB found.

The economic model adopted a conservative approach to estimate the cost-effectiveness of mobile X-ray screening and enhanced case management over a 20 year period. The benefits of interventions that extend lives more than 20 years is ignored, as is any potential reduction in cases of TB more than 20 years into the future. In addition, the model assumed there was no benefit in preventing latent infection that did not progress to active pulmonary disease. For these reasons, it is likely that the interventions described in the model will be more cost effective than estimated.

See appendix G12 for the full report ‘Economic analysis of identifying and managing tuberculosis in hard to reach groups: homeless and prison populations’

9.1.42 Expert Testimony

In addition the programme development group received evidence from a number of experts, these testimonies have been summarised into 10 expert papers; their links to the recommendations are detailed below.

Expert paper 1: 'Service user perspectives'.

Expert paper 2: 'Socio-cultural factors influencing an understanding of tuberculosis within the Somali community in Sheffield'.

Expert paper 4: 'Primary care tuberculosis survey 2010'.

Expert paper 21: 'Screening for tuberculosis and HIV in primary care'.

See appendix G13 for the expert papers summarising the expert testimony.

9.1.5 Fieldwork

Fieldwork aimed to test the relevance, usefulness and feasibility of putting the draft recommendations into practice, fieldwork was conducted during the consultation period. The PDG considered the findings when developing the final recommendations. For details, see appendix G14.

Fieldwork participants who work in TB services or with hard-to-reach groups were overwhelmingly positive about the recommendations and their potential to help identify and manage TB. Many stated that the guidance was an endorsement for prioritising TB prevention and control. It was viewed as a timely document because of concerns about increasing levels of TB.

Participants felt that the recommendations on planning and funding TB services presented an ideal scenario. As such, they did have some reservations about the likelihood of them being implemented in the current economic climate.

See appendix G14 for the 'Fieldwork report: identifying and managing TB among hard to reach groups'

9.1.6 Evidence Statements and Linking Evidence to Recommendations

9.1.6.1 Raising and sustaining awareness of TB among health professionals and those working with hard-to-reach groups

Moderate evidence from two UK studies (both [++]) found that culturally sensitive and appropriate care increased access and adherence to treatment. One sample of African immigrants in the UK found that counselling from healthcare providers, personalised care from specialist nurses, and advice from well-informed peers could improve adherence to treatment. Many women and men from Muslim communities also noted the ability to access gender-compatible services as a facilitator to service access.

Inconsistent evidence from four studies suggests that some participants viewed the standard of care as low. Common themes included feelings of staff being neglectful (HIV patients in respiratory isolation in the USA: one [+]; drug users USA: one [+]) or disrespectful (USA) (one [+]). However, one UK (++) study on Somali immigrants in Sheffield reported that patients were generally happy with their TB services.

Strong evidence from five studies suggests that hard-to-reach groups (mostly African immigrants) have a lack of confidence in or are concerned about misdiagnoses or delayed diagnosis by healthcare professionals. Groups that mentioned these concerns included:

- Somalis in Sheffield (one [++])
- various vulnerable groups including HIV patients in London (one [-])
- African immigrants in London (two [++])
- Somali and Ethiopian immigrants in Norway (one [+]).

Weak evidence from one UK retrospective cohort (-) suggests that screening with a mobile X-ray unit should be offered to all prisoners regardless of symptoms of TB, since limiting

screening to those with symptoms would have missed a substantial number of cases. The conclusions drawn from this study are limited as it looked retrospectively at collected data to calculate how many cases would have been missed if screening had been limited in such a way.

Expert testimony 'Socio-cultural factors influencing an understanding of tuberculosis within the Somali community in Sheffield', 'Primary care tuberculosis survey 2010' and ‘Screening for tuberculosis and HIV in primary care'.

9.1.6.2 Raising and sustaining awareness of TB among hard-to-reach groups

Strong evidence from nine studies suggests that hard-to-reach participants commonly view smoking as a risk factor for or cause of TB. These views were reported by studies with:

- a range of hard-to-reach participants (for example, immigrants, prisoners) in the UK (one [++])
- homeless participants in the USA (two [+])
- mixed immigrant groups in the UK (one [+])
- mixed immigrant groups in Canada (one [++])
- Somali immigrants in the UK (one [++])
- Somali and Ethiopian immigrants in Norway (one [+])
- Asian immigrants (Chinese, Vietnamese) in the UK (one [-]) and the USA (one [-]).

Moderate evidence from five studies reported that participants frequently thought poverty was a condition associated with contracting TB. These views were reported by studies of:

- homeless participants in the USA (one [+])
- mixed immigrant groups in the UK (one [+])
- Somali immigrants in the UK (one [++])
- Somali and Ethiopian immigrants in Norway (one [+]) and Vietnamese immigrants in the USA (one [+]).

Weak evidence from six studies suggests that hard-to-reach participants may consider food or diet-related factors (such as poor diet or unripe/unwashed fruit) to increase the risk of TB. These views were reported by studies of:

- homeless participants in the USA (two [+])
- mixed immigrant groups in the UK (one [+])
- African immigrants in the UK (one [-]) and in Norway (one [+])
- Asian immigrants in the UK (one [-]).

Weak evidence from four studies suggests that hard-to-reach participants may believe that susceptibility to TB is higher when a person has another illness, such as:

- AIDS (homeless people in the USA; one [+])
- low immunity (Asian immigrants in the UK: one [-])
- asthma (Somali immigrants in the UK: one [++])
- pneumonia (African immigrants in the UK: one [++]). In the case of Somali immigrants in the UK, some participants thought that complications in asthma led to TB.

Other factors believed to affect susceptibility have less basis in fact, and yet cannot be claimed to be entirely incorrect, such as lack of self-care, sexual contact, and a hereditary transmission (since mother to infant transmission may occur).

Moderate evidence from seven studies suggests that hard-to-reach participants commonly view lack of self-care ('not looking after yourself') or a health imbalance as risk factors for TB. These views were reported by studies with:

- a range of hard-to-reach participants in the UK (one [++])
- homeless participants in the USA (one [+])
- mixed immigrant groups in the UK (one [+])
- mixed immigrant groups in Canada (one [++])
- Somali immigrants in the UK (one [++])
- Somali and Ethiopian immigrants in Norway (one [+])
- Filipino immigrants in the USA (one [++]).

Moderate evidence from five studies suggests that hard-to-reach participants commonly attribute hereditary causes to TB infection. These views were reported by studies with a range of hard-to-reach and homeless participants in the UK (one [-]); mixed immigrant groups in Canada (one [++]) and New Zealand (one [-]); and African immigrants in the UK (two [++]).

Weak evidence from two studies suggests that hard-to-reach participants may believe that TB could be transmitted through sexual contact. These views were reported by studies with a range of hard-to-reach participants in the UK (one [-]) and mixed immigrant groups in the UK (one [+]).

Weak evidence from two studies suggests that hard-to-reach participants may believe that stress is a cause of TB. These views were reported by studies of Somali immigrants in the UK (one [++]) and Vietnamese immigrants in the USA (one [+]).

Strong evidence from eight studies suggests that hard-to-reach participants commonly view environmental conditions (such as a 'dirty' or 'wet' environment, or weather-related conditions) as a cause of TB. These views were reported by studies with:

- a range of hard-to-reach participants in the UK (one [++])
- homeless participants in the USA (one [+])
- mixed immigrant groups in Canada (one [++])
- Somali immigrants in the UK (one [++] and one [-])
- Asian immigrants (Chinese, Vietnamese, and Filipino) in the UK (two [-] and one [++]).

Moderate evidence from five studies suggests that hard-to-reach participants sometimes consider the sharing of objects such as cigarettes, cutlery, and glasses as a likely transmission mechanism. These views were reported by studies with a range of hard-to-reach participants in the UK (one [-]); homeless people in the USA (two [+]); mixed immigrant groups in the UK (one [+]); and African immigrants in the UK (one [++]). Applicability: five of the 13 studies reviewed here were conducted in the UK, and the rest reported populations of relevance to the UK (for example, Somali and Vietnamese immigrants). We have no reason to believe that the views held by the samples here would not be transferable to populations in the UK.

Weak evidence from two studies indicates that some hard-to-reach groups are unfamiliar with non-symptomatic or latent TB. Some Somali and Ethiopian participants in Norway thought that a lack of symptoms meant that they were healthy (one [+]) and one study explicitly reported no knowledge of latent TB in their sample of various vulnerable groups in London (one [-]).

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Strong evidence from seven studies suggests that participants are aware of the fatality of TB but did not always know whether it was curable. Fatality was discussed by:

- Somali participants in the UK (one [++])
- African immigrants in the UK (one [++])
- various vulnerable groups in the UK (one [-])
- homeless people in the US (one [+]).

Chinese immigrants in the US viewed TB as a curable disease (one [-]), but a lack of understanding about curability was evidenced by African immigrants in the UK (one ++) and homeless people in the USA (one [+]).

Strong evidence from three studies indicated a lack of information or awareness about service availability or access for vulnerable groups in London (one [++]), Somali immigrants in London (one [++]), or Chinese immigrants in New York (one [-]).

Strong evidence from five studies suggests that various hard-to-reach groups felt that fear of death from TB was a barrier to wanting to be screened. This was mentioned by:

- various vulnerable groups in London (one [++])
- Somali immigrants in Sheffield (one [++])
- Filipino immigrants in Hawaii and California (one [++])
- homeless people in San Francisco (one [+])
- homeless people in the North-Eastern US (one [+]).

Strong evidence from three studies shows that language barriers between service users and service providers are a concern for many hard-to-reach immigrant populations. This was evident for Somalis in Sheffield (one [++]); migrant Africans in London (one [++]); and various refugee and minority ethnic groups in New Zealand (one [-]).

Expert testimonty 'Service user perspectives'.

9.1.6.3 Enhanced case management

Moderate evidence from three UK studies (one [-] and two [++]) suggested that the complex social and clinical interactions surrounding a patient with TB can be a challenge to participation and adherence, and that outreach TB link workers or social care workers can facilitate coordination of services.

Strong evidence from four UK studies (all [++]) suggested that healthcare workers find it challenging to meet the complex care needs of hard-to-reach groups with TB, especially where there are cultural and language barriers that make it difficult to interpret symptoms and explain about the disease and its treatment.

Moderate evidence from two randomised controlled trials (RCTs) (both [++], USA) suggest that using peers from the same hard-to-reach group as part of the screening programme can improve screening outcomes for drug users and the homeless. One study found that problem drug users with peers as case managers were more likely to identify contacts than those without such case managers ($p = 0.03$). However, it is not known how much of this difference was due to the staff being former drug misusers or due to the extra case management received. One study found that the homeless with a peer health adviser were more likely to complete screening than those given usual care ($p = 0.004$).

Weak evidence from one USA RCT (+) found that statistically more intravenous drug users were likely to complete treatment if they received peer support (57%) compared with treatment as usual (49%; p less than 0.001), when adherence was measured using electronic bottle caps. However, there was no significant difference when adherence was measured by self-report. All participants received a $10 incentive to adhere to the research protocol, so these adherence rates might not be replicable in settings where such an incentive is not available.

Moderate evidence from one USA RCT (++) found that there was a statistically significant benefit of adding case-management which included an education intervention (8 sessions over 24 weeks) to directly observed preventive therapy (DOPT) to manage latent TB infection in the homeless compared with providing DOPT alone (AOR = 3.01, 95% CI 2.15 to 4.20).

Weak evidence from one USA RCT (+) in intravenous drug users found a statistically significant increase in adherence to treatment completion when a service model approach or social care support was used (59.5%, 95% CI 43.6 to 75.3) compared with treatment as usual (13.1%, CI 3.0% to 23.7%; p less than 0.0001) but no difference compared with DOPT plus methadone maintenance without additional social care support (p values not reported). The study was limited due to baseline differences between groups and the generalisability of the findings was limited because different daily doses of isoniazid were prescribed.

Weak evidence from one USA before-and-after study (+) found a statistically significant increase in treatment completion rates in favour of service model approach or social care support compared with treatment as usual (p less than 0.001) in mixed hard-to-reach groups with latent TB infection (service model approach or social care support = 70.3%, 102/145 vs. treatment as usual = 47.9%). The study was mainly limited by baseline differences between groups and there may have been treatment contamination across the two time periods.

Weak evidence from one Spanish before-and-after study (-) suggests that adherence among prisoners who were smear-positive increased significantly over time, both before and after DOT was introduced, rising from 95 per 100 in 1993 to 100 per 100 in 2000 for those who received DOT, and from 60 per 100 in 1987 to 76 per 100 in 1992 for those who received treatment as usual. There was also no information reported on the sample characteristics.

Moderate evidence from one USA before-and-after study (+) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with DOT alone (OR = 5.73, 95% CI 2.25 to 14.84) in a population that included over 50% of drug users. The study was limited because DOT was compared with a retrospective cohort of patients.

Moderate evidence from one Spanish before-and-after study (+) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with self-administered therapy (RR = 3.07, 95% CI 2.13 to 4.41) in mixed hard-to-reach groups. The study was limited because DOT was compared with a retrospective cohort of patients and there were significant differences between the cohorts in the two time periods.

Moderate evidence from one USA RCT (++) found that the probability of completing treatment was statistically greater when peers delivered enhanced case management to drug users compared with limited case management delivered by a healthcare worker (RR = 2.68, 95% CI 1.24 to 5.82; p = 0.01). The conclusions drawn from these findings were limited because the peer-led intervention also had enhanced case management. It is therefore not known how much of the positive treatment outcomes were due to the healthcare worker who delivered the service or the intensity of case management.

9.1.7 Recommendations

See section 9.2.7

9.2 Adherence and treatment completion [2015]

9.2.1 Clinical introduction

Sub-optimal uptake of, and adherence to, tuberculosis treatment for people with active or latent TB can lead to increased morbidity and mortality, increased infectiousness, and the emergence of drug resistance.

9.2.2 Review questions

What case management strategies and interventions are effective in increasing the uptake of, or adherence to, treatment for people with active or latent TB?

What is known from studies of case management interventions about the barriers to uptake and adherence to treatment for active or latent TB?

What information, education or other support based interventions are currently used in practice to support the diagnosis, treatment and management of TB?

What is the effectiveness and cost-effectiveness of education, information and support to increase the uptake of, or adherence to, treatment for people with active or latent TB?

9.2.3 Evidence review

The reviews for these questions were developed both internally (by NICE CPH) and externally (by the London School of Hygiene and Tropical Medicine)

For each review question, a separate search strategy was developed and undertaken and included a number of different databases (please see each individual review for details of the search strategy, the databases searched, and inclusion and exclusion criteria). The evidence from the included studies relating to each review question has been critically appraised and quality ratings assigned according to the Centre for Public Health Methods Manual 2012 (3rd Edition), the full evidence tables and quality rating summaries for each review can be found in appendix G

Each review (where relevant) includes all evidence statements derived from the included studies, the evidence statement section below only includes the evidence statements which underpin the updated recommendations made by the committee. Included above are those evidence statements which underpin the incorporated recommendations from public health guidance 37 (PH37).

For full evidence tables, quality ratings and all evidence statements derived from the evidence reviewed for PH37 see reviews 1–4 here (or in appendix G):

- PH37 Tuberculosis - hard-to-reach groups: supporting evidence

9.2.3.1 Case-management

Clinical review

For this review question, papers were identified from a range of databases (Applied Social Sciences Index and Abstracts (ASSIA), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Database of Systematic Reviews (CDSR), Cochrane Health Technology Assessment database (HTA), Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Science & Humanities, Database of Abstracts of Reviews of Effects (DARE), Embase EPPI Centre Trials Register of Promoting Health Interventions (TRoPHI), Education Resource Information Center (ERIC), Health Management Information Consortium (HMIC), MEDLINE in Process,

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MEDLINE, OpenGrey, Science Citation Index Expanded, Social Policy and Practice (SPP), Social Sciences Citation Index, Sociological Abstracts (SA) and non-database sources (British Infection Association via http://www.britishinfection.org/drupal/, British Thoracic Society via http://www.brit-thoracic.org.uk/, Campbell Collaboration via http://www.campbellcollaboration.org/, Chartered Institute of Environmental Health via http://www.cieh.org/, Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register, Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/, Health Protection Scotland via http://www.hps.scot.nhs.uk/, Health Quality Improvement Partnership via http://www.hqip.org.uk/, Infection Prevention Society via http://www.ips.uk.net/, Local Government Association via http://www.local.gov.uk, McMaster University Health Evidence via http://www.healthevidence.org/, National Guideline Clearinghouse http://www.guideline.gov/, NICE via http://www.nice.org.uk/, Public Health England via https://www.gov.uk/government/organisations/public-health-england, Public Health Observatory via http://www.apho.org.uk/, Stop TB UK via http://www.stoptbuk.org/, Target Tuberculosis via http://www.targettb.org.uk, TB Alert via http://www.tbalert.org).

Google was searched using a simplified version of the search string, and the advanced search options to limit to PDFs or word document files. The first 100 search results were scanned for relevance. The review team also searched PubMed using a time-limited search to identify any new items.

The searches were limited from 1993 to the most recent records (with the exception of the Conference Proceedings Citation Indexes, which were run from 2011 to the present).

In addition the review team considered submissions in response to the NICE Call for Evidence (July 2013) and supplementary searching was undertaken to identify evidence, identified as relevant to the review using records selected for inclusion through the screening process.

The supplementary searching was conducted in three ways:

- Backwards reference harvesting: studies were extracted from the bibliographies of the papers identified (one generation) and added to Reference Manager if the titles were relevant and they were not methodology papers (e.g. the Cochrane Handbook).
- Forwards citation searching: Web of Science and Google Scholar. All citations were added to Reference Manager
- BL Ethos (http://ethos.bl.uk/) to identify unpublished theses

The search strategy was designed to identify papers relating to outcome evaluations including but not limited to randomised, quasi-randomised and non-randomised control trials, cohort studies, case-control studies and case series were included where applicable to the criteria in the review. In addition qualitative studies which reported views or barriers and facilitators about an intervention were sought.

Studies were excluded if:

- The population did not include people with active or latent TB
- The population studied was not from a country which is a current OECD member
- The intervention was not aiming to increase uptake or adherence, or did not measure uptake of, or adherence to, tuberculosis treatment as an outcome.
- The intervention did not include case management (CM), defined as ‘an intervention where a designated case manager works with an individual patient, including directly observed therapy, with or without other CM components’.
- The intervention was purely educational or informational.
- Interventions delivered by non-professionals without specific training in CM were excluded.

Update 2015

- The study was not reported in English
- Qualitative studies about views of TB in general, or about ongoing practice in TB treatment or TB services, were excluded.

From a database of 3796 unique abstracts, 187 full-text articles were assessed for eligibility and 30 studies were included in the review (13 effectiveness studies, 16 cost-effectiveness studies, and two views studies, with one study in two categories). In the effectiveness element of the review of the 13 included studies 6 were rated high quality (++), 2 medium (+) and 5 low (–); in the 2 qualitative studies 1 was rated medium quality (+) and 1 low (–).

Health economic review

For this element of the review question, papers were identified from a range of databases and other sources using three methods.

1. The following sources were searched using the validated cost effectiveness filter from the Centre for Reviews and Dissemination applied:

- Embase via OVID
- MEDLINE in Process via OVID
- MEDLINE via OVID

2. ASSIA, EThOS, BNI, CINHAL, CENTRAL, CDSR, HTA, DARE, EPPI, ERIC, HMIC, OpenGrey, SCO, SPP, SA and the websites listed below were not searched again. All of the results from these resources were added to both the cost effectiveness files.

3. The following resources were used to identify additional cost-effectiveness papers:

- CEA Registry via https://research.tufts-nemc.org/cear4/
- EconLit via Dialog
- EconPapers via http://econpapers.repec.org/
- Health Economic Evaluations Database (HEED) via http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- NHS Economic Evaluations Database (NHS EED) via http://www.thecochranelibrary.com

As above the same supplementary searching methods were used:

- Backwards reference harvesting
- Forwards citation searching
- Related item searching using

The search strategy was designed to identify all papers relating to cost-effectiveness studies (either modelling or economic evaluations) applicable to the criteria in the review. The same exclusion criteria as the effectiveness study was used.

In the cost-effectiveness element of the review, of the 16 included studies 1 was rated high quality (++), 5 medium (+) and 9 low (–). At the QA stage 1 study (Chaulk et al., 2000), was found to be not applicable; in line with the methods guide, this study was not data-extracted or considered further in the analysis.

The findings below are categorized by population or setting type, in the following categories:

- Patients with active TB (N=9 studies)
- Drug users (N=3)
- People with latent TB infection (N=1)
- Migrants or new entrants (N=1)
- Neonates (N=1)

Update 2015

As with the effectiveness evidence, the focus of the majority of the cost-effectiveness studies (N=13) is DOT (with, in some cases, incentives and enablers); only two could be said to incorporate elements of ECM (Jit et al., 2011 (+); Porco et al., 2006 (++)).

The majority of the studies quantify cost-effectiveness in terms of net cost savings, i.e. the (healthcare) costs of the intervention compared to the healthcare costs of the cases of TB and drug-resistance averted by the intervention the costs of treatment failures and relapses averted, rather than to the impacts of TB on patients and others. Few cost-effectiveness studies are analysed in terms of cost per QALY or other cost-utility measures (as usually recommended by NICE) and still fewer incorporate any measure of the broader social costs of TB. In addition, all the cost-effectiveness studies use static models; none attempt to model transmission dynamics and the likely impacts of this on cost-effectiveness.

See appendix G2 for the detailed summary tables of quality assessment, evidence tables and review in full.

9.2.3.24 Information, education and support that is currently in use

This review question was assessed by the Centre for Public Health, in accordance with the Methods for the development of NICE public health guidance (Third Edition). The review focused on UK-related practice examples of information, education or other support offered to support testing, diagnosis, treatment and management of tuberculosis (TB).

For this review, studies were identified from a number of different databases (Applied Social Sciences Index and Abstracts (ASSIA) via ProQuest, British Library Electronic Theses Online (EThOS), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Database of Systematic Reviews (CDSR), Cochrane Health Technology Assessment database (HTA), Database of Abstracts of Reviews of Effects (DARE), Embase, EPPI Centre Database of Education Research, EPPI Centre Trials Register of Promoting Health Interventions (TRoPHI), Education Resource Information Center (ERIC), Health Management Information Consortium (HMIC), MEDLINE in Process, MEDLINE, OpenGrey, Social Care Online (SCO), PsycINFO, Social Policy and Practice (SPP), Sociological Abstracts (SA) and non-database sources (Campbell Collaboration via http://www.campbellcollaboration.org/, McMaster University Health Evidence via http://www.healthevidence.org/, National Guideline Clearinghouse via http://www.guideline.gov/, NICE via http://www.nice.org.uk/, NICE Evidence Search via https://www.evidence.nhs.uk/, Public Health Observatory via http://www.apho.org.uk/, Public Health England via https://www.gov.uk/government/organisations/public-health-england, Turning Research Into Practice via http://www.tripdatabase.com/, African Health Forum via http://www.africanhealthforum.org.uk/index.htm, Black Health Agency via http://www.thebha.org.uk, British Infection Association via http://www.britishinfection.org/drupal/, British Society for Antimicrobial Chemotherapy via http://bsac.org.uk, British Thoracic Society via http://www.brit-thoracic.org.uk/, Centers for Disease Control and Prevention resources on TB via http://www.cdc.gov/tb/, Chartered Institute of Environmental Health via http://www.cieh.org/, Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register, Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/, Education for Health via http://www.educationforhealth.org/, Health Protection Scotland via http://www.hps.scot.nhs.uk/, Health Quality Improvement Partnership via http://www.hqip.org.uk Infection Prevention Society via http://www.ips.uk.net, Local Government Association via http://www.local.gov.uk/, Public Health Wales via http://www.publichealthwales.wales.nhs.uk/, Race Equality Foundation via http://www.raceequalityfoundation.org.uk, South Asian Health Foundation via http://www.sahf.org.uk, Stop TB UK via http://www.stoptbuk.org/, Target Tuberculosis via http://www.targettb.org.uk/, TB Alert via http://www.tbalert.org). In addition the review team considered submissions in response to the NICE Call for Evidence (July 2013). Study types

such as Randomised, quasi-randomised and non-randomised control trials, cohort studies, case-control studies and case series were included where applicable to the criteria in the review on effectiveness of information, education and support described below. (See appendix C for the full review protocol).

Papers were excluded if:

- Population not of interest
  - not TB
  - setting not in scope
- Not a description of practice
- No description of information, education or support (no information of interest reported)
- paper is a letter or editorial
- outcomes reported, not associated with an information, awareness raising, education or support intervention
- Other exclusion: Not available, thesis or duplicate

From a database of 2764 unique records, 150 full-text papers were assessed and 22 papers met the inclusion criteria including academic papers, evaluation reports and leaflets. Of the 144 exclusions, these were assessed not to describe: practice (80); information, education or support (36) or a population of interest (13). There were 15 'other' exclusions (including 12 which were not available, a thesis or duplicate)

Following further review and discussion with the GDG [chairs], a collection of 6 records was created by selecting the more detailed and likely applicable descriptions of practice. In addition a number of leaflets were identified that were designed to raise awareness in the public about TB, these were reviewed by lay members of the GDG against a set of questions with feedback provided to the GDG verbally.

See appendix G5 for a summary list of questions GDG lay members considered when providing verbal feedback on patient leaflets, videos and comments received and to review the leaflets provided.

See appendix G5 for the evidence tables and review summary in full

9.2.3.3 Effectiveness of information, education and support

A range of information, education and support approaches are currently employed in practice in the UK to support the testing, diagnosis, treatment, management, prevention and control of TB among relevant groups. These are summarised (where evidence has been identified) in the separate review report current information education and support practice in the UK conducted for this guidance (see appendix G5).

For this review question, papers were identified from a range of databases (Applied Social Sciences Index and Abstracts (ASSIA) via ProQuest, British Library Electronic Theses Online (EThOS), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Database of Systematic Reviews (CDSR), Cochrane Health Technology Assessment database (HTA), Database of Abstracts of Reviews of Effects (DARE), Embase, EPPI Centre Database of Education Research, EPPI Centre Trials Register of Promoting Health Interventions (TRoPHI), Education Resource Information Center (ERIC), Health Management Information Consortium (HMIC), MEDLINE in Process, MEDLINE, OpenGrey, Social Care Online (SCO), PsycINFO, Social Policy and Practice (SPP), Sociological Abstracts (SA) and non-database sources (Campbell Collaboration via http://www.campbellcollaboration.org/, McMaster University Health Evidence via http://www.healthevidence.org/, National Guideline Clearinghouse via http://www.guideline.gov/, NICE via http://www.nice.org.uk/, NICE Evidence Search via https://www.evidence.nhs.uk/, Public Health Observatory via

Update 2015

http://www.apho.org.uk/, Public Health England via https://www.gov.uk/government/organisations/public-health-england, Turning Research Into Practice via http://www.tripdatabase.com/, African Health Forum via http://www.africanhealthforum.org.uk/index.htm, Black Health Agency via http://www.thebha.org.uk, British Infection Association via http://www.britishinfection.org/drupal/, British Society for Antimicrobial Chemotherapy via http://bsac.org.uk, British Thoracic Society via http://www.brit-thoracic.org.uk/, Centers for Disease Control and Prevention resources on TB via http://www.cdc.gov/tb/, Chartered Institute of Environmental Health via http://www.cieh.org/, Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register, Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/, Education for Health via http://www.educationforhealth.org/, Health Protection Scotland via http://www.hps.scot.nhs.uk/, Health Quality Improvement Partnership via http://www.hqip.org.uk Infection Prevention Society via http://www.ips.uk.net, Local Government Association via http://www.local.gov.uk/, Public Health Wales via http://www.publichealthwales.wales.nhs.uk/, Race Equality Foundation via http://www.raceequalityfoundation.org.uk, South Asian Health Foundation via http://www.sahf.org.uk, Stop TB UK via http://www.stoptbuk.org/, Target Tuberculosis via http://www.targettb.org.uk/, TB Alert via http://www.tbalert.org/). In addition supplementary searching was undertaken

Supplementary searching:

Two sets were selected for supplementary searching to identify effectiveness and cost effectiveness evidence, which included:

- Items identified through the call for evidence and scoping searches prior to the database searching
- Items identified as relevant to the review using records selected for inclusion through the screening process.

The supplementary searching was conducted in three ways:

- Backwards reference harvesting: studies were extracted from the bibliographies of the papers identified and added to Reference Manager if the titles were relevant and they were not methodology papers (e.g. the Cochrane Handbook).
- Forwards citation searching: the Science Citation Index and the Social Science Citation Index via Web of Science (http://apps.webofknowledge.com) were used to look for later papers citing the references of interest. All citations were added to Reference Manager
- Related item searching using PubMed - the first 100 references (sorted by relevance) were downloaded via http://www.ncbi.nlm.nih.gov/pubmed/

The search strategy was designed to identify papers relating to outcome evaluations including but not limited to randomised, quasi-randomised and non-randomised control trials, cohort studies, case-control studies and case series and cost-effectiveness studies were included where applicable to the criteria in the review. In addition the review team considered submissions in response to the NICE Call for Evidence (July 2013).

Studies were excluded if:

- The population did not have or were not suspected to have, or be at increased risk of infection from and/or progression to active disease.
- The intervention did not include an outcome evaluation of a strategy or intervention providing and delivering information and/or education about:
  a. the symptoms and risk of TB
  b. clinical management of the illness
  c. broader social support for people affected by TB?

Update 2015

- The outcomes did not report a change in knowledge or awareness; uptake of diagnostic testing or uptake and adherence to treatment/management of TB as an outcome?
- The study was not conducted in a high-income country (that is, a current OECD member)
- The study was published before 1998

From a database of 8160 unique abstracts, 185 full-text articles were assessed for eligibility and 26 studies were included in the review (25 effectiveness studies and one cost-effectiveness study); 9 were rated high quality (++), 7 medium (+) and 10 low (–).

The review was carried out using systematic methods, with extensive searching, a priori inclusion criteria, and full quality assessment and data extraction according to the NICE methods manual. However, there may be some limitations.

See appendix G6 for the detailed summary table of quality assessment (Table 1 effectiveness studies), evidence tables and review in full

9.2.45 Evidence statements

9.2.4.16 Case-management

Effectiveness of case management and directly observed preventive therapy (DOPT) for drug users on treatment uptake, adherence and completion [ES2]

There is weak evidence from one US study (–) that a policy of directly observed preventive therapy (DOPT) showed a non-statistically-significant trend towards lower rates of TB among drug users compared to self-administered preventive therapy (one-group RR 0.4 [0.04-4.8]).

There is conflicting evidence from two (++) US studies as to whether DOPT leads to higher adherence rates than self-administered therapy (SAT) among drug users. There is strong evidence from one (++) US study that DOPT does not lead to higher completion rates, or adherence rates, than usual care with SAT among drug users (completion 80% against 79%; adherence 82% against 90% [for 80% adherence], 80% against 77% [for 90% adherence]). However, DOPT did lead to higher adherence rates than usual care for 100% adherence (77% against 10%, p<0.001), and to higher adherence rates than a peer support intervention (80% against 51% [for 90% adherence], p < 0.001; 77% against 6% [for 100% adherence], p<0.001).

There is strong evidence from one (++) US study that DOPT combined with methadone treatment leads to higher rates of TB treatment completion among heroin-dependent injecting drug users than usual care with SAT (77.1% against 13.1%, p < 0.0001). However, an additional case management component with counselling and service access did not increase the effectiveness of the basic intervention (59.5% completion).

There is strong evidence from one (++) US study that either outreach DOPT with incentives or on-site DOPT with incentives improve adherence among drug users more than outreach DOPT alone, but outreach DOPT with incentives is not significantly different from on-site DOPT with incentives (OR for outreach DOPT with incentive vs outreach DOPT alone 29.7 (56.5–134.5); OR for on-site DOPT with incentive vs outreach DOPT alone 39.7 (58.7–134.5)).

There is strong evidence from one (++) Estonian study that an intervention involving incentives, scheduling visits and reminders, and providing transport, increases attendance at a TB clinic among drug users (57.1% against 30.4%, p = 0.004).

Update 2015

The evidence is partially applicable to people in the UK who use drugs. This is because the populations of drug users in the studies, or the services available to them, may differ from those in the UK.

Effectiveness of case management and observed drug collection for migrants or new entrants on treatment uptake and completion [ES4]

There is weak evidence from one (–) US study that cultural case management, including culturally tailored education and support by trained peers, leads to higher uptake of treatment (88% against 73%, p<0.001) and completion of treatment (82% against 37%, p<0.001) for latent tuberculosis infection (LTBI) among refugee populations.

There is weak evidence from one (–) Italian study that requiring immigrants to attend clinic sites to collect drugs for LTBI treatment leads to lower rates of treatment completion (7.3% against 26%, p=0.006).

The evidence is partially applicable to immigrants to the UK. This is because the populations of migrants in the studies, or the policies in place around immigration, may differ from those in the UK.

Effectiveness of DOT for people with HIV on treatment completion [ES5]

There is medium evidence from one (+) US study[1] that DOT leads to higher rates of treatment completion than SAT for LTBI treatment among people with HIV (93% against 61%, p < 0.001). However, this study also involved a change in regimen.

The evidence is directly applicable to people in the UK. Despite differences in the broader healthcare context in the USA, there are no obvious differences in the population, context or setting of the study compared to the UK context.

Effectiveness of education and tracking for homeless people on treatment completion [ES5}

There is strong evidence from one (++) US study[1] that an education programme and active tracking of defaulters, with DOT and incentives, leads to higher rates of completion of LTBI treatment among homeless people than DOT and incentives alone (adjusted OR 3.01 (2.15-4.20), p < 0.001).

The evidence is partly applicable to people in the UK. This is because the population of homeless people in the study, or the services available to them, may differ from those in the UK.

Qualitative evidence on interventions to promote adherence to treatment for TB or LTBI [ES12]

There is weak evidence from one (–) UK study[1] that a link worker for marginalized people with TB or LTBI is viewed positively by staff in other agencies. Participants report that the link worker increases understanding of TB among workers in different services, facilitates peoples' access to different services and provides practical and emotional support.

There is medium evidence from one (+) Australian study[2] that a videophone DOT service is viewed positively by staff and patients. The privacy and convenience of the videophone DOT service were especially valued.

Update 2015

Cost-effectiveness of DOT, increased outpatient care, and Find and Treat for patients with active TB [ES7]

There is medium evidence from five (3 + and 2 –) cost-effectiveness studies[1-5] that directly observed therapy for active TB incurs lower net costs than self-administered therapy, when the cost savings resulting from reduced treatment failure are taken into account. Relative net cost savings from DOT in these studies[1,4-5] range from US$1,788 to US$16,370 per patient treated (with other studies reporting a relative cost per death averted of US$1,234[2], and a relative cost per patient cured of US$2,783[3]).

However, there is weak evidence from one (–) cost-effectiveness study[6] that DOT is more costly than SAT for patients at low risk of default (incremental cost of US$919 per patient treated, US$40,260 per patient cured). There is also moderate evidence from one (+) study that a policy of universal DOT is more costly than a policy of partial DOT (incremental cost of US$24,064 per patient cured).[3]

There is medium evidence from one (+) cost-effectiveness study[7] that a Find and Treat service which combines mobile screening for high-risk populations with enhanced case management support has an incremental cost-effectiveness compared to usual care of £6,400 per QALY (£18,000 per QALY for mobile screening and £4,100 per QALY for enhanced case management).

There is weak evidence from one (–) cost-effectiveness study that a policy of increased outpatient care for TB is less costly than usual care (cost savings of US$10,804 for smear-positive patients, US$9,028 for smear-negative per patient cured), although the addition of DOT and incentives makes little difference to this.

There is weak evidence from one (–) cost-effectiveness study[9] that remote DOT via videophone has an incremental cost-effectiveness of Aus$1.32 per day of observation, compared to in-person DOT.

The evidence is partially applicable to the UK context as the data utilised in the studies which provide the cost-effectiveness evidence appear, with one exception, to come from non-UK sources. There may be barriers to applicability resulting from differences in clinical practice, populations or settings, or healthcare funding systems.

Cost-effectiveness of active case findig for Latent TB and DOPT for drug users [ES8]

There is weak evidence from three (1 +1 and 2 –2,3) cost-effectiveness studies that programmes for drug users which include screening and directly observed prophylactic therapy have lower relative net costs than no intervention, with net cost savings ranging from US$3,724 to US$30,770 per case averted, or from US$1,380 to US$3,590 per person treated1-3.

The applicability of this evidence to the UK context is unclear as it is not clearly reported where the data utilised in the studies which provide the cost-effectiveness evidence are derived from other than the US. There are therefore likely to be multiple reasons to question the applicability of the findings.

Cost-effectiveness of DOT for people with latent TB infection [ES9]

There is weak evidence from one (–) cost-effectiveness study1 that weekly isoniazid and rifapentine under DOT is cost saving compared to no intervention, while twice-weekly isoniazid under DOT has an incremental cost-effectiveness ratio of $7,879 per QALY compared to no intervention.

Update 2015

The applicability of this evidence to the UK context is unclear as it is not clearly reported where the data utilised in the studies which provide the cost-effectiveness evidence are derived from. There is therefore reason to question the applicability of the findings.

9.2.4.26 Information and education that is currently in use

Practice around information education and support was broadly grouped into six categories [SS1]

- Awareness raising of TB, linked to annual and or national campaigns.
- Information on medication and nutrition for patients plus general and targeted information for providers.
- Education practice including peer review against national guidelines, the inclusion of TB content in medical training for GPs.
- Establishment of TB networks as a mode of support for practitioners.
- Social care/outreach workers supporting patients
- Support (general) including

Awareness raising of TB, linked to annual and or national campaigns [SS2]

Practice Nurses expressed a need for more information on how to raise awareness in the communities in which they practice (TB National Knowledge Service 2013)

UK survey therefore directly applicable to UK practice.

Information on medication and nutrition for patients [SS3]

A mixture of preferences for mode and frequency of provision were reported for providers, including ad hoc arrangements. The evidence was elicited from practitioners who deliver the service and people with or who have had TB examining their experience and perceptions of services available. (Belling 2012 and Boudioni et al. 2011).

Limited sample size, but in depth evaluation directly applicable to UK practice.

Education practices [SS4]

Education practices were diverse and included peer review against national guidelines, the inclusion of TB content in medical training for GPs (Bothamley et al, 2011 , survey of PCTs and TB clinics). Survey of users' experience (n=10) suggested GP awareness and a low 'index of suspicion' of TB may be topics to address through education (Boudioni et al, 2011)

UK based survey and in depth evaluation therefore directly applicable to UK practice.

Establishment of TB networks as a mode of support for practitioners [SS5]

Establishment of TB networks was reported in all the 8 major UK cities in which the service audit and evaluation took place. (Bothamley et al, 2011).

UK based service evaluation therefore directly applicable to UK practice.

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Social care/outreach workers supporting patients [SS6]

The outcomes of surveys of service user and providers indicated that linking with nurses, a social outreach model of care and (non medical) social care and outreach staff for supported patients with practical (accommodation, benefits, transport) social as well as psychosocial aspects and also could 'free-up' clinical staff to concentrate on clinical TB work, rather than support the social needs of people (Belling et al., 2012; Boudioni et al, 2011; Craig 2008) The skill mix for these roles spanned clinical, social health, management, education and 'administrative' (including research) skills (Belling et al. 2012)

The survey were developed and delivered in the UK therefore are directly applicable to UK practice.

Support (general) [SS7]

Support (general) captures a number of overarching aspects of elements of practice that have been shown to be beneficial in improving awareness and supporting socially complex cases to engage with services and complete treatment including

- the provision of key workers for each person with TB;
- educational outreach;
- Link workers: piloting of a social outreach model of care involving link working between providers as well as between provider and service users. Support from link workers included:
  - establishing trust,
  - assistance with housing/accommodation,
  - accessing benefits and
  - addressing the impact of the psychosocial aspects of TB

Applicability: all studies were UK based and are therefore directly applicable to UK practice.

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9.2.4.3 Effectiveness of information and education

Effectiveness of information and education for immigrants and refugees on TB knowledge, clinic attendance and treatment adherence [ES1]

There is weak evidence from three studies that information and education for immigrants and refugees are effective in improving a range of TB-related outcomes.

There is weak evidence from one (–) US study[1] that a culturally tailored intervention, with continuity of care, is effective in increasing adherence among Latino immigrants (157 total pills taken against 129 pills taken in control arm, p=0.028).

There is weak evidence from one (–) US study[2] that an educational video is effective in improving knowledge (82.3% against 56.1%, p<0.001) and self-efficacy about TB (89.7% against 72.8%, p<0.001) among immigrants and refugees attending an education centre.

There is weak evidence from one (–) Australian study[3] that an information and community media campaign promoting TB services is effective in improving knowledge about TB (significant improvement in 3 of 5 outcomes).

The evidence is partly applicable to immigrants and refugees in the UK, because the populations in the studies may differ from those in the UK.

1 Ailinger et al., 2010 (–)

2 Wieland et al., 2013 (–)

3 Sheikh and MacIntyre, 2009 (–)

Effectiveness of educational interventions for prisoners on treatment uptake and completion [ES2]

There is moderate evidence from three studies that educational interventions are effective in increasing uptake of and adherence to treatment among prisoners.

There is strong evidence from one (++) US study[1] that ongoing education for prisoners, compared to a single education session, increases attendance rates at TB clinics after release (37% against 24%, significance NR) and treatment completion rates (23% against 12%, adjusted OR 2.2 [1.04-4.72]).

There is moderate evidence from one (+) US study[2] that a single education session given by research assistants is more effective than a session given by discharge planners in increasing attendance rates at TB clinics after release (33% against 15%, RR 0.79 [0.68-0.92], p=0.001) and in increasing completion rates among those who attend the clinic (47% against 28%, p=0.049).

There is strong evidence from one (++) US study[3] that a single session of education combined with incentives for prisoners is no more effective than education alone in increasing attendance rates at TB clinics after release (25.8% against 23.3%, OR 1.43 [0.35-3.71], p=0.82).

The evidence is partly applicable to prisoners in the UK, because the populations in the studies, and the prison settings, may differ from those in the UK.

1 White et al., 2002 (++)

2 White et al., 2005 (+)

3 White et al., 1998 (++)

Effectiveness of educational interventions for patients with active TB on treatment adherence [ES8]

There is moderate evidence from two studies, one (+) South Korean[1] and one (+) Turkish[2], that educational interventions are effective for patients with active TB. One study[1] finds that education and reminders increase rates of treatment completion or cure (91.6% against 75%, RR 1.23 [1.12-1.36]), and another[2] that an educational programme increases attendance rates (54% against 29%, p<0.01) and adherence (80% against 42%, p<0.001).

The evidence is partially applicable to people with active TB in the UK, because the populations in the studies may differ from those in the UK.

1 Kim et al., 2009 (+)

2 Clark et al., 2007 (+)

Effectiveness of information, education and reminders for TB-related outcomes [ES11]

The evidence indicates that information, education and reminders are effective in improving TB-related outcomes, although very brief interventions may not be effective.

There is moderate evidence from seven studies that informational or educational interventions[1-4], reminders[5], and interventions combining education and reminders[6,7], are effective in promoting adherence-related outcomes in a range of populations. There is also weak evidence from two studies[8,9] that educational interventions are effective in improving knowledge or attitudes.

There is evidence that such interventions are ineffective from two studies[10,11]. However, in both these studies the intervention is of minimal intensity (respectively a single 5- to 10-minute educational session, and a short letter).

No study in this group was conducted in the UK. The evidence is partly applicable to the UK, because there may be differences in the populations or settings.

1 Ailinger et al., 2010 (–)

2 Clark et al., 2007 (+)

3 Hovell et al., 2003 (+)

4 White et al., 2005 (+)

5 Ozuah, 2001 (–)

6 Boom et al. 2000 (+)

7 Kim et al., 2009 (+)

8 Sheikh and MacIntyre, 2009 (–)

9 Wieland et al., 2013 (–)

10 Malotte et al., 1999 (++)

11 Taubman et al., 2013 (++)

Interventions for service providers [ES13]

The evidence indicates that intensive interventions with service providers, integrating clinician education with other components such as reminders, incentives and process improvement, are effective in improving service delivery outcomes. However, the evidence on educational interventions alone is mixed and inconclusive.

There is strong evidence from two studies that integrated multi-component interventions with an educational element are effective in improving TB screening rates[1,2]; one study shows more mixed results, but is of poor quality[3].

There is weak evidence from one study that computer-generated reminders to physicians are effective in increasing TB screening rates[4].

There is weak and mixed evidence from four studies regarding the effectiveness of education or information alone for service providers with respect to knowledge outcomes[5-8]. No studies investigate such interventions with respect to service delivery outcomes.

Four studies in this category are from the UK; however, three of these measure knowledge outcomes only. The remainder of the evidence is partly applicable to clinicians working with people with TB in the UK, because the populations and contexts of service delivery in the studies may be different from those in the UK.

1 Griffiths et al., 2007 (++)

2 Margolis et al., 2004 (++)

3 Udeagu et al., 2007 (–)

4 Steele et al., 2005 (–)

5 Roy et al., 2011 (–)

6 Roy et al., 2008 (–)

7 Fiefield, 2007 (–)

8 Maetz et al., 1998 (–)

9.2.5 Collation of related NICE guidance - recommendations on awareness raising and the provision of information to the public (information, education and support)

Relevant NICE recommendations on the topic of Information/Education and Support with reference to research question NN & OO in the Tuberculosis update scope were collated. This was developed in response to a request by the GDG. This was not meant to be an

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exhaustive process but to give an idea of any relevant recommendations across a variety of guideline the identified guidance included both clinical and public health guideline (n=9)

The guidance topic may or may not relate directly to TB, the committee were asked to consider this when reviewing the information presented. The purpose of providing this information was to enable the GDG to consider the results from the reviews detailed above within the context of the wider literature and other recommendations NICE make on information, education and support across a variety of health topics. Triangulating this information with the results from the review(s) facilitated validation of data through cross verification with multiple sources.

The associated section and recommendations were provided as a whole from each guideline. The GDG was informed that it was only one or more of the recommendations or sub-bullets are applicable to Tuberculosis, but to ensure the relevant parts are in context to the whole recommendation or section, it has be inserted verbatim.

For detailed information on who the actors for each recommendations are, and the evidence behind the recommendations please follow the URL links below:

Medicines Adherence: Involving patients in decisions about prescribed medicines and supporting adherence (CG76) http://publications.nice.org.uk/medicines-adherence-cg76

Key principles section and

- Section 1.1 Patient involvement in decisions about medicines
- Section 1.2 Supporting adherence
- Section 1.3 Reviewing medicines
- Section 1.4 Communication between healthcare professionals

Resources: https://www.nice.org.uk/guidance/cg76/resources/medicines-adherence-patient-information-resource-a-template-for-display-in-healthcare-settings

Evidence statements Evidence extractions and Economic evidence extractions

Reducing differences in the uptake of immunisations (PH21) http://www.nice.org.uk/PH21

- Recommendation 1: evidence statements 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 38, 39, 40, 41, 47, 48, 49, 51, 52, 55, 61; IDE
- Recommendation 2: IDE
- Recommendation 3: evidence statements 25, 26, 27, 28; IDE
- Recommendation 4: evidence statements 20, 41; IDE
- Recommendation 5: evidence statements 16, 43, 48, 49, 51
- Recommendation 6: 66; IDE

Evidence statements - http://publications.nice.org.uk/reducing-differences-in-the-uptake-of-immunisations-ph21/appendix-c-the-evidence#evidence-statements
Evidence reviews - http://guidance.nice.org.uk/PH21/SupportingEvidence

Skin cancer prevention: information, resources and environmental changes (PH32) http://www.nice.org.uk/PH32

- Recommendation 1: evidence statement ER3.31; additional evidence: expert paper 2 and 3; economic analysis report 1 and 2; IDE
- Recommendation 2: evidence statements ER3.34, ER5.1, ER5.5, ER5.6, ER5.16, ER5.18, ER5.25, ER5.34, ER5.48, ER5.51, ER5.53; additional evidence: expert paper 2, 3, 4, 5, 6 and 7; economic analysis report 1 and 2; IDE

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- Recommendation 3: evidence statements ER3.2, ER3.5, ER3.10, ER3.27, ER3.28, ER3.32, ER3.33, ER5.16, ER5.18; additional evidence: expert paper 1, 4, 5 and 6
- Recommendation 4: evidence statements ER3.2, ER3.5, ER3.6, ER3.9, ER3.10, ER3.12, ER3.13, ER3.14, ER3.15, ER3.16, ER3.17, ER3.18, ER3.19, ER3.20, ER3.23, ER3.24, ER3.25, ER3.27, ER3.28, ER3.29, ER3.31, ER3.32, ER5.2, ER5.4, ER5.5, ER5.6, ER5.8, ER5.9, ER5.10, ER5.11, ER5.12, ER5.13, ER5.14, ER5.15, ER5.16, ER5.17, ER5.19, ER5.20, ER5.21, ER5.22, ER5.23, ER5.24, ER5.26, ER5.27, ER5.28, ER5.30, ER5.31, ER5.35, ER5.36, ER5.38, ER5.44, ER5.45, ER5.47, ER5.48, ER5.51, ER5.53, ER5.57, ER5.58, ER5.60, ER5.61, ER5.62, ER5.63, ER5.64, ER5.65, ER5.67; additional evidence: expert papers 2, 3, 4, 5, 6 and 7; economic analysis report 1 and 2; IDE
- Recommendation 5: evidence statements ER3.21, ER3.23, ER3.33, ER5.29, ER5.31, ER5.32, ER5.33, ER5.36, ER5.39, ER5.41, ER5.42, ER5.50, ER5.59; additional evidence: expert papers 2, 5 and 6; IDE
- Recommendation 6: evidence statements ER3.22, ER4.1, ER4.2, ER4.5, ER5.41, ER5.53; additional evidence: economic analysis report 2; IDE

Evidence Statements http://publications.nice.org.uk/skin-cancer-prevention-information-resources-and-environmental-changes-ph32/appendix-c-the-evidence#evidence-statements

Evidence Reviews http://guidance.nice.org.uk/PH32/SupportingEvidence

Increasing the uptake of HIV testing among Black Africans in England (PH33)
http://www.nice.org.uk/PH33

- Evidence statement numbered Q indicates that the linked statement is numbered 4 in review 2, 'Increasing the uptake of HIV testing to reduce undiagnosed infection and prevent transmission among black African communities living in England – barriers to HIV testing'
- Recommendation 1: evidence statements Q1.2, Q1.3, Q1.4, Q4.3, Q 7.1, Q7.2, Q7.3, Q7.4; IDE
- Recommendation 4: evidence statements Q1.2, Q1.3, Q1.4, Q4.2, Q 4.3, Q5.1; IDE

Evidence Statements http://publications.nice.org.uk/increasing-the-uptake-of-hiv-testing-among-black-africans-in-england-ph33/appendix-c-the-evidence#evidence-statements

Evidence Reviews http://guidance.nice.org.uk/PH33/SupportingEvidence

Increasing the uptake of HIV testing among men who have sex with men (PH34)
http://www.nice.org.uk/PH34

- Evidence statement number 7 indicates that the linked statement is numbered 7 in the review 'Preventing and reducing HIV transmission among men who have sex with men'.
- ER 1 indicates that the expert report 'Time to test for HIV: expanded healthcare and community HIV testing in England. Interim report' is linked to a recommendation
- Recommendation 2: evidence statements 3, 8, 9, 10, 12, 13, 18; IDE
- Recommendation 3: evidence statement 4, 16, 18; ER1; IDE
- Evidence Statements http://publications.nice.org.uk/increasing-the-uptake-of-hiv-testing-among-men-who-have-sex-with-men-ph34/appendix-c-the-evidence#evidence-statements
- Evidence Reviews http://guidance.nice.org.uk/PH34/SupportingEvidence

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Preventing type 2 diabetes - risk identification and interventions for individuals at high risk (PH38) http://www.nice.org.uk/PH38

- Recommendation 2: evidence statements 1.1, 1.5, 1.6, 1.7, 4.1, 4.3, 4.4, 4.5, 4.11, 4.12; Additional evidence: expert paper 1, expert paper 6, commissioned report
- Recommendation 15: Additional evidence: commissioned report; IDE
- Recommendation 16: Additional evidence: commissioned report; IDE
- Recommendation 18: evidence statements 1.7, 3.2, 3.3, 3.8, 4.1, 4.3, 4.4, 4.5, 4.6, 4.7, 4.17, 4.18; Additional evidence: commissioned report; IDE
- Evidence statements http://publications.nice.org.uk/preventing-type-2-diabetes-risk-identification-and-interventions-for-individuals-at-high-risk-ph38/appendix-c-the-evidence#evidence-statements
- Evidence reviews http://guidance.nice.org.uk/PH38/SupportingEvidence

Smokeless tobacco cessation: South Asian communities (PH39) http://www.nice.org.uk/PH39

- Recommendation 2: Evidence statements 16, 17, 18.
- Recommendation 3: IDE
- Recommendation 4: Additional evidence (West et al. 2004).
- Recommendation 5: Evidence statements 2, 3, 5, 33, 34, 42.
- Recommendation 6: Evidence statements 27, 43, 44.
- Evidence statements http://publications.nice.org.uk/smokeless-tobacco-cessation-south-asian-communities-ph39/appendix-c-the-evidence#evidence-statements
- Evidence reviews http://guidance.nice.org.uk/PH39/SupportingEvidence

Hepatitis B and C - ways to promote and offer testing (PH43) http://www.nice.org.uk/PH43

- Recommendation1: evidence statements: Q1, Q2, Q3, Q4, Q5, Q8, Q9, Q10, E1; IDE
- Recommendation2: evidence statements: Q1, Q2, Q3, Q4, Q5, Q8, Q9, Q10, Q14, Q15, Q16, Q23, Q28, Q29, E1; IDE
- Recommendation3: evidence statements: Q2, Q18, Q20, Q21, Q28, Q29, Q30, E2, E5, E8; IDE
- Recommendation6: evidence statements: Q18, Q20, Q21, Q24, Q25, Q28, Q29, Q30, E1, E4, E5, E6, E7, E8, E9; IDE
- Evidence statements http://publications.nice.org.uk/hepatitis-b-and-c-ways-to-promote-and-offer-testing-to-people-at-increased-risk-of-infection-ph43/appendix-c-the-evidence#evidence-statements
- Evidence reviews http://guidance.nice.org.uk/PH43/SupportingEvidence

Behaviour change: individual approaches (PH49) http://www.nice.org.uk/PH49

- Evidence statement number 1.1 indicates that the linked statement is numbered 1 in review 1. Evidence statement number 2.1.3 indicates that the linked statement is numbered 1.3 in review 2. Evidence statement number 3.3.4 indicates that the linked statement is numbered 3.4 in review 3. EP1 indicates that expert paper 1 is linked to a recommendation
- Recommendation 12: evidence statements: 3.3.1–3, 3.2.1, 3.2.2, 3.3.1–9, EP5, EP10–12
- Recommendation 13: EP5, EP10–12

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- Evidence statements http://publications.nice.org.uk/behaviour-change-individual-approaches-ph49/the-evidence#how-the-evidence-and-expert-papers-link-to-the-recommendations
- Evidence reviews http://guidance.nice.org.uk/PH49/SupportingEvidence

9.2.5.15 Synthesis

In summary the following components of information, education and support were identified across multiple related guidelines:

- Tailored, involve target audience in development and piloting, disseminate appropriately i.e. culturally specific radio or TV, shelters, community venues etc…
- Include: Risks & benefits, how to access services and support, dispel myths, position testing and treatment as responsible and empowering, use phrasing that enhances people's belief they can change.
- Keep it simple and succinct, use a variety of formats: print, electronic, audio, pictorial, braille, text messaging. Ensure language is appropriate and considers cultural and religious beliefs.
- Provide longer appointments, walk-in clinics, mobile outreach, home visits and ensure you address both social and practical barriers
- Recruit and train peers from relevant communities
- Ensure all training (peers and HCW), includes communication skills, ability to answer questions, also brief interventions and how to support behaviour change.
- Include training as part of CPD and ensure it meets a national minimum standard and where possible is included in or is designed equivalent of core curriculum.

9.2.6 Evidence to recommendations

Relative value of different outcomes	The GDG discussed the evidence received in particular in relation to outcomes observed in different population groups compared with those observed in general population interventions. In relation to outcomes presented in the effectiveness review of information education and support, it was recognised that studies tended to consider people 'lost to follow-up' as 'non completers' and the GDG chair noted that the outcome 'treatment completion' (across all the studies) was subjective. The GDG noted that the optimum outcome measures are 'cured' and 'measured adherence'.
Trade-off between benefits and harms	The GDG discussed changing the original recommendation in CG117 which covered DOT but made no mention of the full tailored package of care that may be needed for adherence in groups at highest risk. The GDG wished to make it clear that DOT should not be viewed as simply watching someone take their treatment but a method for improving adherence in those groups most likely to be non-compliant. The GDG noted that DOT should be considered as an integral part of case management in complex cases such as those with the risk factors/groups listed in recommendations on adherence. This package of care is called 'enhanced case management' in this guideline. They discussed whether it was feasible to extrapolate PH37 recommendations (recommendation 15 in this case) to enable them to be incorporated in the updated clinical guideline. The GDG highlighted the need to ensure that enhanced case management, including directly observed therapy (DOT) was considered the standard of care for the general population for improving adherence, but they recognised that it was not necessarily the best option for everyone (for example those who may prefer self-administered therapy (SAT) because of work or other commitments). Although the GDG agreed that outcomes would be improved if everyone received enhanced case management including DOT, they recognised that individual preference and the current financial climate within health services was also likely to reduce application of this recommendation. Therefore, the recommendation on enhanced case management defines a number of groups that may be considered at greatest need of enhanced case management including

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DOT, and also includes it as a treatment for anyone who requested it irrespective of their personal or social circumstances

The GDG wished to include a statement saying that enhanced case management including DOT 'must' be used in the groups at risk of default' as outlined in this recommendation. This was based on a combination of their own experience and expertise as well as the evidence available from the literature. However, the GDG recognised that the published evidence base alone was not powerful enough to make this recommendation and there was also potential for such a statement to be misconstrued as implying a legal duty thus, their wish to make a 'must' recommendation in this manner needed to be down played. However, despite some of the limitations in the evidence the GDG remain convinced that this should be a strong recommendation in NICE style (i.e. 'offer' rather than 'consider') given their experience of the benefits of this type of intervention in practice.

The GDG discussed children with TB and those that may be at greatest risk of non-adherence. It was agreed that any children of the groups associated with likelihood of non-compliance (outlined in the recommendation on enhanced case management) were also likely to be at risk of non-adherence. The GDG therefore extrapolated from the evidence statements relating to this recommendation to ensure that children in these circumstances were not marginalised inadvertently.

Whilst there was some evidence on Directly Observed Preventative Therapy for those with Latent TB (DOPT/LTBI) it was predominantly in drug users, despite the evidence for DOT showing that this type of intervention is valuable in other higher risk social groups and the general population the GDG did not feel that they were able to extrapolate this evidence from active TB to include LTBI in all populations. However, the GDG did feel that further consideration of this question was needed especially in light of the increasing risk of LTBI in some population groups. They agreed this gap in the evidence was important, and may result in a research recommendation.

The GDG discussed whether creating schemes for certain sub-groups could be deemed discriminatory but acknowledged that this would depend if adherence is low at baseline. To this end, the GDG added a consensus recommendation to re-evaluate the need for enhanced case management and DOT regularly to determine whether a step up or step down approach was needed due to circumstance or other changes indicated likelihood of adherence had changed from initial assessment, resulting in the need for an updated care plan.

Monetary and other incentives for people at risk of TB were discussed by the GDG based on the evidence available from the reviews. The GDG considered that the evidence indicated that incentives were of value in improving outcomes but because this evidence was a by-product of the search rather than a systematically identified element they could not be certain that all relevant evidence had been presented. As a result no additional details on incentives than those included in PH37 or CG117 could be proposed. It was noted that this would be a useful area for future research within the UK context because the majority of evidence appeared to be in non-UK settings that may limit direct applicability to the UK context, thus applicability of this evidence was an additional consideration in not making recommendations in relation to incentives. The GDG was also mindful that: the review team had not specifically undertaken a search for incentives and all the key studies may not have been identified; the evidence for incentives should refer to PH37; and need to be wary of diverting away from tailored package of care

The GDG took into consideration the input of lay members, specifically their evaluation of how information to patients could be delivered. The lay members' views, the value they placed on having information available in the course of their illness, and their feedback on examples of practice leaflets and videos were considered throughout the discussions. The following elements were considered

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	to be important: face to face contact and culturally appropriate materials to be made available in a range of formats (leaflets and videos). The GDG discussed these factors at length and suggested that these could be captured in a recommendation on information for patients In relation to the review on current practice in the UK of information, education or support processes, the GDG noted that there was not a consistent approach to how information and education is presented. The GDG recognised that information needs should to be considered for 3 subgroups: the patients (both at risk and those who are diagnosed), link or other support workers, and healthcare workers. The level of the education for these groups may need to differ as described elsewhere in this table. The GDG considered the evidence for education/information interventions and noted that there was evidence for both active and latent groups. They noted that the evidence was equivocal in some groups namely healthcare workers and people who take drugs. The GDG noted that for education the intensity of the education matters, therefore, in healthcare workers who already have good levels of knowledge you are less likely to see large changes from an education programme, but people such as prisoners do seem to receive measurable benefits. This is not to say that healthcare workers should not receive education, but that the size of effect may be affected because of their underlying knowledge of this or associated areas. Thus it is important that any education delivered is appropriately challenging and if the level of the educational component is increased (i.e. difference between prior knowledge and target for knowledge attainment following the intervention was increased), then the impact of educational interventions may be more apparent in those with a good underlying knowledge
Trade-off between net health benefits and resource use	The GDG noted that the evidence base for cost effectiveness was mixed and ranged from moderate to weak. Despite this potential limitation in the quality of the evidence, it was numerous and consistent and showed that in groups at risk of default DOT was cost effective. In those at low risk of default DOT was seen to be not cost effective. The GDG's expert consensus, experience and knowledge of the impact of DOT in particular groups was consistent with this evidence on cost effectiveness. The GDG noted that there was no evidence for cost-effectiveness for broader peer support or education. Overall however, as the recommendations made were not new but a combination of published recommendations from previous guidelines (Namley CG117 and PH37) and as the review and economc evidence presented had done nothing to pursuade them to update these recommendations with respect to their intent or meaning, the commitee did not consider cost effectiveness other than to note it further supported the combined recommendations from PH37 and CG117.
Quality of evidence	The GDG noted that despite any gaps noted the evidence base was broad and ranged from weak to strong. Despite these limitations in the quality of the evidence, the GDG viewed that their expert consensus and experience would be a substantive part of the evidence base for the development of the recommendations. The GDG discussed the incorporation of Public Health Guidance 37 recommendations developed using the Centre for Public Health methods and processes by a Programme Development Group (PDG) made up of their peers. It was noted that a significant proportion of the current GDG were members of the PH37 guidance development committee, and that all the GDG had confidence in the methods, processes and validation of NICE guidance. They therefore decided they did not feel the need to review the evidence on which PH37 recommendations had been developed and to accept the quality ratings, evidence

reviews and evidence statements associated with all incorporated recommendations. Further it was noted that the reviews for PH37 had been developed, critically appraised and presented to the committee using the same methods and processes as the reviews on which the updated adherence recommendations were based, which they considered robust and appropriate to the topic. Furthermore, the evidence presented (in the reviews in appendix G4-6) was broadly consistent with the recommendations in PH37 so there was no evidence to significantly revise the recommendations or make new ones. Instead the GDG adapted the previous recommendations by amalgamating them with the clinical guidance and extrapolating them to the general population, in particular those on raising and sustaining awareness in professionals and the public.

Incentives was discussed again at the GDG meeting in April 2014, because the GDG received further evidence on incentives and noted that the evidence suggests this helps with drug users' attendance. It was noted that this would be a useful area for future research within the UK context because the majority of evidence appeared to be in non-UK settings that may limit direct applicability to the UK context, thus applicability of this evidence was an additional consideration in not making recommendations in relation to incentives.

The GDG noted a concern about the generalisability of the studies included in the effectiveness review on information, education and support interventions - this was related to their concern on the low uptake. The GDG noted that the quality of evidence for education interventions was acceptable. However, they noted the studies assessing peer support were appraised as of low methodological quality.

The GDG chair noted that the outcome 'treatment completion' (across all the studies) was subjective

The GDG noted a weakness in the evidence base on the effectiveness of information, education and support interventions for people who are alcohol misusers. Because this group is considered at high risk from low levels of treatment completion this was considered an issue. However, on further discussion of whether a research recommentaion may be appropriate here the GDG agreed that this particular sub-group may cut across the others where evidence was available namely homless people, drug users, and prison populations and that a recommendation for research in this area may be confounded by co-existing risk factors .

In relation to the information, education and support practice review, the GDG noted the complexities of the review (including grey literature) and that descriptions of practice were limited to UK based studies for practical purposes. They would have been interested to hear about practice in other countries but recognised that its applicability would have been very limited in particular when taking into account background policy and healthcare financing and access issues.

The GDG also received evidence on recommendations on information, education and support from other pieces of NICE guidance. They considered this evidence as an additional source for triangulation against the comments received from the lay members on the current literature available from some NHS organisations, as well as their own experience of what is available in the field along with the sample videos presented to the GDG during the meeting. The GDG agreed that the information available from wider NICE guidance topics further corroborated what they had heard and their own knowledge and enabled them to make clear recommendations on the 'Content and format of information for the public about TB – recommendation 8.6. Furthermore, the variability observed in the quality, quantity and suitability of the information presented resulted in the committee agreeing that a collaborative approach between national organisations to produce generic and locally adaptable source materials was appropriate and was likely to lead to quality improvement across the UK.

In relation to the practice review on information, education and support , the GDG noted that there was not a consistent approach to how information and education is presented.

The GDG highlighted that all the interventions considered were heavily context and content specific, and that what works may be highly variable in different

	situations, populations and countries. The GDG therefore noted that a broad range of interventions will be needed, not just one thing alone. The GDG agreed that there is a need for much clearer evidence on the effectiveness of DOPT for improvements in LTBI treatment completion in populations other than drug users. They therefore developed a research recommendations on DOPT relating to the need for trials in all relevant population groups or highlighted this area as a gap in the available evidence. The GDG discussed the lack of consistency in the evidence available for review, the personal experience of committee members and knowledge of effective interventions in other relevant cities (namely New York) regarding peer support interventions. The GDG remained convinced of the validity and effectiveness of this approach, but recognised there were gaps in the evidence and developed research recommendations on this area or highlighted it as a gap in the evidence. It was considered particularly important in this area for both quantitative and qualitative recommendations due to the nature of the intervention, they extrapolated this to include the need for effectiveness of non-clinical support workers (see recommendations on non-clinical support workers) due to the inclusion of recommendations in the service organisation section of the guideline.
Other considerations	The GDG considered the evidence presented for the effectiveness review (3b) and noted that the evidence was primarily available for 4 subsets of population (prisons, drug users, people who are homeless and migrants) and for 4 main types of intervention (education, counselling, peer support/coaching and incentives). The GDG was mindful that for studies with multicomponent interventions, it was not feasible to extract the absolute effect of a single element such as peer support. This would mean the package was separated artificially and there would be no way of determining how the benefits of a package of care, work synergistically to improve outcomes if they looked at components of care in isolation. The GDG noted that the effectiveness evidence for peer support not being effective came from LTBI. This is important as people with active TB who actually have symptoms are likely to respond differently than people with LTBI. The GDG was mindful that they did not have any evidence on whether peer support is effective for certain groups with active TB. However, they also noted that they had no evidence that it was ineffective in active TB. The GDG noted a gap in evidence on peer support in the migrant population but their collective experience suggested that immigrants with active TB may benefit from peer or other non-clinical support. Therefore the GDG considered this could be an area for future research. In relation to the review of information, education and support practice in the UK , the GDG acknowledged the challenge in summarising information captured in the grey literature. The GDG also noted that there could potentially be overlap with the service organisation recommendations elsewhere in this guideline (for example TB networks). The GDG had a brief discussion about the level of detail needed for recommendations on the content of educational or information packages. They discussed adverse or other events and side effects, how TB can occur in people not deemed at increased risk the importance of remaining vigilant for signs and symptoms, whether key signs and symptoms needed setting out in the recommendation and the need for ongoing education in disciplines with a high turnover. They also discussed the use of effective methods for communicating with GPs such as update days and whether to recommend that local medical schools should be encouraged to include TB in the curriculum systematically. The GDG recognised that no evidence on information or education content had been systematically appraised, but they wanted to note that these were important considerations for multidisciplinary TB teams to include in the development of any education, information or support packages produced. The GDG noted that the cross referencing work of other NICE recommendations for providing information education or support to a variety of population groups supported the details and suggestions from lay members as well as the

information from the reviews. They found this element of the evidence presented particularly useful as it was based on published NICE recommendations that had been developed according to the methods and processes of NICE and in line with accepted consultation and transparency requirements by NICE. They felt this added a certain level of quality to the recommendations provided and further supported their consensus on the subject of information for the public.

Update 2015

9.2.71 Recommendations

2 ***Improving adherence: case management including directly observed therapy***

3 **149. Allocate a named TB case manager to everyone with active TB as soon as**
4 **possible after diagnosis (and within 5 days). The clinical team should tell each**
5 **person who their named TB case manager is and provide contact details. [2006,**
6 **2012 amended 2015]**

7 **150. The TB case managers should work with the person diagnosed with TB to**
8 **develop a health and social care plan, and support them to complete therapy**
9 **successfully. The TB case manager should:**

10 • offer an incident risk assessment to every person with TB, to identify their needs and
11 whether they should have enhanced case management including directly observed
12 therapy
13 • educate the person about TB and the treatment
14 • develop an individual care plan after discussion with the person
15 • gain the person's consent to the plan and agree a review date (for example, when
16 moving from initiation to maintenance, or at each contact to ensure the person's
17 needs are being met)
18 • coordinate discharge planning, especially for people on directly observed therapy
19 • involve representatives from other allied professions and key workers from all
20 organisations who work with the person if appropriate
21 • explore appropriate ways that peers and voluntary organisations can provide support.
22 **[2006, 2012, amended 2015]**

23 **151. Offer directly observed therapy as part of enhanced case management in**
24 **people who:**

25 • do not adhere to treatment (or have not in the past)
26 • have been treated previously for TB
27 • have a history of homelessness, drug or alcohol misuse
28 • are currently in prison, or have been in the past 5 years
29 • have a major psychiatric, memory or cognitive disorder
30 • are in denial of the TB diagnosis
31 • have multidrug-resistant TB
32 • request directly observed therapy after discussion with the clinical team
33 • are too ill to administer the treatment themselves. **[2012, amended 2015]**

34 **152. In children whose parents are members of any of the above groups, offer**
35 **directly observed therapy as part of enhanced case management and include**
36 **advice and support for parents to assist with treatment completion. [2015]**

Update 2015

Update 2015

153. Re-evaluate the need for directly observed therapy throughout the course of TB treatment whenever the person's (or in the case of children, parents') circumstances change. [new 2015]

154. TB case managers should ensure the health and social care plan (particularly if directly observed therapy is needed) identifies why a person may not attend for diagnostic testing or follow a treatment plan, and how they can be encouraged to do so. It should also include ways to address issues such as fear of stigmatisation, support needs and/or cultural beliefs, and may include information on:

- demographics (for example, age, nationality, place of birth, length of time in UK)
- all current prescribing regimens
- housing needs and living situation, including looked-after children
- substance misuse (drugs or alcohol)
- any contact with the criminal justice system
- the need for hepatitis B and C or HIV testing
- HIV status
- other health conditions (physical or mental)
- communication factors (for example, language and literacy levels)
- ability to access treatment (mobility and transport needs)
- employment or entitlement to benefits
- legal or immigration status (including risk of removal or relocation within the UK)
- any enablers or incentives to overcome anything that is stopping diagnosis or treatment. **[2012, amended 2015]**

155. The health and social care plan should:

- state who will be observing treatment and where (if the person is having directly observed therapy this should be provided at a location that is convenient and accessible to them, for example, at a methadone clinic) **[2012, amended 2015]**
- include actions to take if contact with the person is lost (for example, keeping details of people who might be able to help re-establish contact) **[2012]**
- refer to, and be coordinated with, any other care plan already established for the person **[2012]**
- define the support needed to address any unmet health and social care needs (for example, support to gain housing or other benefits, or to help them access other health or social care services) **[2012, amended 2015]**
- include a commitment from the person to complete their TB treatment **[2012, amended 2015]**
- be supported by frequent contact with any key workers who work with the person. **[2006 amended 2011, amended 2015]**

156. Multidisciplinary TB teams should aim to find people with active TB who are lost to follow-up, or who stop using services before completing diagnostic investigations. They should report all those lost to follow-up to local Public Health England teams, GPs, the referring organisation and specialist outreach teams. [2012]

Other strategies to encourage people to follow their treatment plan

157. To encourage people to follow their treatment plan, involve people in treatment decisions for active or latent TB from the start. Emphasise the importance of following the treatment plan when agreeing the regimen. [2015]

Update 2015

158. Multidisciplinary TB teams should implement strategies for active and latent TB to encourage people to follow the treatment plan and prevent people stopping treatment early. These could include:

- reminder letters, printed information, telephone calls, texts and apps using an appropriate language **[2006, amended 2015]**
- health education counselling and patient-centred interviews **[2006, amended 2015]**
- tailored health education booklets from quality sources **[2006, amended 2015]**
- home visits **[2006]**
- random urine tests and other monitoring (for example, pill counts) **[2006]**
- access to free TB treatment for everyone (irrespective of eligibility for other NHS care) and information about help with paying for prescriptions **[2006, 2012, amended 2015]**
- social and psychological support (including cultural case management and broader social support) **[new 2015]**
- advice and support for parents and carers **[new 2015]**
- incentives and enablers to help people follow their treatment regimen. **[new 2015]**

Update 2015

159. TB control boards should ensure services take into account the barriers facing vulnerable migrants who may need treatment, and in particular the stigma they may face. Other issues include the location of services (both geographically and in terms of opening times) and people's language and cultural needs, in terms of the format of advice and the type of information given. [2012, amended 2015]

Strategies in prisons or immigration removal centres

160. On arrival at a prison or immigration removal centre, healthcare professionals should ask all prisoners and detainees (including those being transferred from other establishments) whether they are taking TB medication, to ensure continuity of treatment. [2012]

161. All prisoners and immigration removal centre detainees having treatment for active TB should have a named TB case manager. The case manager should be responsible for contingency planning for discharge from prison or detention. [2012]

162. Prisons and immigration removal centres should ensure multidisciplinary TB staff have access to prisoners and detainees who need treatment (for example, by being given security clearance). [2012]

163. All prisoners having treatment for active TB should have directly observed therapy. [2012]

164. Prison health services should have contingency, liaison and handover arrangements to ensure continuity of care before any prisoner on TB treatment is transferred between prisons or released. In addition, other agencies working with prisoners or detainees should also be involved in this planning. [2012]

165. Prison and immigration removal centre healthcare services should liaise with the named TB case manager (from the multidisciplinary TB team) to ensure

contingency plans for continuation of treatment are drawn up for prisoners and immigration removal centre detainees with TB. [2012]

166. Multidisciplinary TB teams should ensure accommodation is available for the duration of TB treatment after the prisoner or detainee's release. [2012]

167. Multidisciplinary TB teams should ensure directly observed therapy is arranged for prisoners or detainees being treated for TB after their release. This should be available close to where they will live in the community. [2012]

Raising and sustaining awareness of TB

Among health professionals and those working with at-risk groups

168. Multidisciplinary TB teams (in collaboration with Public Health England, primary care, the voluntary sector and Health Education England) should identify and support an ongoing TB education programme for local professionals in contact with the general public, and at-risk groups in particular. This includes, for example, staff in emergency departments, GPs and wider primary care staff, people who work in housing support services, staff who support migrants and those working in walk-in centres, hostels, substance misuse projects and prisons. [2012, amended 2015]

169. Multidisciplinary TB teams should ensure the education programme increases other professionals' awareness of the possibility of TB and reduces the stigma associated with it. The programme should include detail on:

- causes of TB, how it is transmitted, and the signs and symptoms
- lifestyle factors that may mask symptoms
- local epidemiology, highlighting under-served groups, other high-risk groups and the fact that TB also occurs in people without risk factors
- principles of TB control:
    - early diagnosis and active case-finding
    - how to support treatment (including directly observed therapy)
    - drug resistance
    - awareness of drug interactions (including factors such as effect on contraception efficacy)
    - contact investigation after diagnosing an active case
    - the importance of adhering to treatment
    - treatment for TB is free for everyone (irrespective of eligibility for other NHS care)
    - social and cultural barriers to accessing health services (for example, fear of stigma and staff attitudes)
    - local referral pathways, including details of who to refer and how
    - the role of allied professionals in awareness-raising, identifying cases and helping people complete treatment
    - misinformation that causes fear about TB, including concerns about housing people with the condition
    - the best ways to effectively communicate all the above topics with different groups. **[2012, amended 2015]**

170. Statutory, community and voluntary organisations and advocates working with the general public, and under-served and high-risk groups in particular, should share information on TB education and awareness training with all frontline staff. (They should get information on this from the local multidisciplinary TB team.) [2012, amended 2015]

171. If possible, statutory, community and voluntary organisations should ensure peers from under-served groups and anyone else with experience of TB contribute to, or lead, awareness-raising activities. (Peers who lead such activities will need training and support.) [2012, amended 2015]

Among at-risk groups

172. Multidisciplinary TB teams should help professionals working in relevant statutory, community and voluntary organisations to raise awareness of TB among under-served and other high-risk groups. These professionals should be able to explain that treatment for TB is free and confidential for everyone (irrespective of eligibility for other NHS care). They should also be able to provide people with details of:

- how to recognise symptoms in adults and children
- how people get TB
- the benefits of diagnosis and treatment (including the fact that TB is treatable and curable)
- location and opening hours of testing services
- referral pathways, including self-referral
- the potential interaction of TB medication with other drugs, for example, oral contraceptives and opioids (especially methadone) and HIV treatment
- TB/HIV co-infection
- how to address the myths about TB infection and treatment (for example, to counter the belief that TB is hereditary)
- how to address the stigma associated with TB
- the risk of migrants from high-incidence countries developing active TB – even if they have already screened negative for it
- contact tracing. **[2012, amended 2015]**

173. Multidisciplinary TB teams and others working with at-risk groups should use high quality material to raise awareness of TB (see section 1.1.2). [2012, amended 2015]

174. Multidisciplinary TB teams and others working with the general public, and with under-served and other high-risk groups in particular, should include information on TB with other health-related messages and existing health promotion programmes tailored to the target group. [2012, amended 2015]

175. Multidisciplinary TB teams should work in partnership with voluntary organisations and 'community champions' to increase awareness of TB, in particular among under-served groups at risk of infection but also in the general population. If possible, peers who have experience of TB should contribute to awareness-raising activities and support people in treatment. [2012, amended 2015]

Providing information for the public about TB

176. National organisations (for example, National Knowledge Service – Tuberculosis, TB Alert, Public Health England, Department of Health and NHS Choices) should work together to develop generic, quality-assured template materials with consistent up-to-date messages. These materials should be made freely available and designed so that they can be adapted to local needs. [new 2015]

177. Multidisciplinary TB teams should use these templates for general awareness raising and targeted activities in under-served and other high-risk groups. Involve the target group in developing and piloting the materials. [new 2015]

178. The content of any materials should:

- be up-to-date and attractively designed, including pictures and colour where possible
- be culturally appropriate, taking into account the language, actions, customs, beliefs and values of the group they are aimed at
- be tailored to the target population's needs
- include risks and benefits of treatment, and how to access services, advice and support
- dispel myths
- show that, by deciding to be tested and treated for TB, a person can be empowered to take responsibility for their own health
- use language that encourages the person to believe that they can change their behaviour
- be simple and succinct. **[new 2015]**

179. Make the material available in a range of formats such as written, braille, text messages, electronic, audio (including podcasts), pictorial and video. Make them freely available in a variety of ways, for example, online, as print materials or on memory sticks. [new 2015]

180. Disseminate materials in ways likely to reach target groups, for example, via culturally specific radio or TV stations, at shelters, and at community, commercial or religious venues that target groups attend regularly. [new 2015]

Update 2015

Strategies in prisons or immigration removal centres

See recommendations 160 – 167

9.2.8 Research recommendations

14. Strategies to improve treatment completion in those infected with latent TB infection and at risk of non-adherence

Is Directly Observed preventative Therapy (DOPT) and other support strategies effective and cost effective compared self-administered therapy in promoting the uptake of and adherence to treatment in those populations who should be offered DOT as part of enhanced case management for active TB?

Why this is important

Effectively treating people with latent TB is considered a cornerstone of TB control. Supporting people at risk of non-adherence to treatment is therefore vital to these

efforts. Despite this, little evidence was identified on the effectiveness or cost effectiveness of DOPT in groups at high risk of non-adherence. Randomised controlled trials in these populations should be conducted.

15. Support strategies to improve treatment completion in those infected with active TB

Are peer support workers, non-clinical support workers effective and cost effective compared self-administered therapy and traditional clinical staff (i.e. TB nurses) in reducing time to diagnosis, promoting diagnostic testing uptake, adherence to treatment and improving contact tracing in under-served and high risk groups. What barriers and facilitators can impact on the effectiveness and cost effectiveness of these interventions?

Why this is important

The GDG noted that there was evidence that various support strategies using trained peers or non-clinical staff were effective in supporting TB control efforts although there was non-available from the UK. They also noted there was no consistent evidence comparing these outcomes to normal care (i.e. TB control nurses) or self-administered therapy, or in assessing the cost effectiveness of these interventions to normal care. Further, there was no systematic information on the barriers and facilitators that may affect these outcomes when comparing clinical and non-clinical staff in delivering the same interventions. The GDG considered these interventions to be of particular importance to under-served and high risk groups. Randomised controlled trials and qualitative assessment of the impact in these populations should be conducted.

10 Service organisation

10.1 'Identifying and managing tuberculosis among hard-to-reach groups' [PH37]

This chapter briefly captures the evidence on which Public Health guideline 37 (PH37) 'Tuberculosis- hard-to-reach groups' was based. Some of the recommendations from this guideline have been incorporated into the service delivery guidance being consulted on in this section (others have been incorporated elsewhere in the guideline). The following five sub-headings provide a brief overview of the evidence on which NICE public health guideline 37 is based and that was reviewed by a committee the programme development group (PDG) using the Public Health process and methods to develop recommendations. These recommendations may have subsequently been adapted for inclusion into this guideline 'Tuberculosis-Update' NGXXX.

'Tuberculosis - hard-to-reach groups' (PH37) was developed to improve the way tuberculosis (TB) among hard-to-reach groups was identified and managed. It was for commissioners and providers of TB services and other statutory and voluntary organisations that work with hard-to-reach groups.

The main groups considered were:

- people who are homeless
- substance misusers
- prisoners
- vulnerable migrants.

The recommendations covered:

- strategic oversight and commissioning of TB prevention and control activities
- raising and sustaining awareness of TB among health professionals and those working with hard-to-reach groups - and among the hard-to-reach groups themselves
- local needs assessment
- cohort review
- commissioning multidisciplinary TB support
- identifying and managing TB (including contact investigations)
- rapid-access TB services and enhanced case management
- the provision of accommodation during treatment.

10.1.1 Evidence Reviews (including Health Economic Reviews) from PH37

Four reviews were commissioned to inform the development of guidance on Tuberculosis - hard to reach groups, as follows

Review 1: 'Tuberculosis evidence review 1: Review of barriers and facilitators'

Review 2: 'Evidence review on the effectiveness and cost effectiveness of interventions aimed at identifying people with tuberculosis and/or raising awareness of tuberculosis among hard-to-reach groups'

Review 3: 'Evidence review on the effectiveness and cost effectiveness of interventions aimed at managing tuberculosis in hard-to-reach groups'

Review 4: 'Evidence review on the effectiveness and cost effectiveness of service models or structures to manage tuberculosis in hard-to-reach groups'

See appendix G8-11 for the full reviews including quality assessments and evidence tables for all included studies.

10.1.23 Economic Analysis (PH37)

The economic analysis looked at the cost effectiveness of using mobile X-ray screening and enhanced case management - combined and separately - to identify and manage TB among homeless and prison populations. This was compared with current practice. The analysis also estimated the number of cases of pulmonary TB that would be averted due to earlier detection.

The results indicate that the interventions are most cost effective among populations with the highest prevalence of TB. Likewise, the benefit of ensuring treatment is completed is greater among those at high risk of transmitting TB (that is, among groups where TB prevalence is highest).

The recommendations for vulnerable migrants are largely based on existing NICE guidance (clinical guideline 117).

Estimates of cost per quality-adjusted life years (QALY) are presented for mobile X-ray screening. They are expressed as a threshold analysis (not as a cost per QALY) for enhanced case management and for mobile X-ray screening combined with enhanced case management. Sensitivity analyses were performed on key parameters, including prevalence of disease.

The economic analysis indicated how much it is worth spending to raise treatment completion rates from 55% to 75% among two separate populations: 10,000 homeless people and10,000 prisoners. It is based on the assumption that the NHS and other government bodies would be prepared to spend up to £20,000 to gain one QALY. The results suggest that it would be cost effective to spend an estimated £21,000 extra per additional case found among homeless people, when the prevalence of TB among this group is 778 cases per 100,000. For a prison population with a prevalence of 208 cases per 100,000, it would be cost effective to spend an additional £35,000 per additional case of active TB found.

The economic model adopted a conservative approach to estimate the cost-effectiveness of mobile X-ray screening and enhanced case management over a 20 year period. The benefits of interventions that extend lives more than 20 years is ignored, as is any potential reduction in cases of TB more than 20 years into the future. In addition, the model assumed there was no benefit in preventing latent infection that did not progress to active pulmonary disease. For these reasons, it is likely that the interventions described in the model will be more cost effective than estimated.

See appendix G12 for the full report 'Economic analysis of identifying and managing tuberculosis in hard to reach groups: homeless and prison populations'

10.1.38 Expert Testimony (PH37)

In addition the programme development group received evidence from a number of experts, these testimonies have been summarised into 10 expert papers; their links to the recommendations are detailed below.

PH37: Expert paper 1: 'Service user perspectives'

PH37: Expert paper 2: 'Socio-cultural factors influencing an understanding of tuberculosis within the Somali community in Sheffield'

PH37: Expert paper 3: 'Screening international migrants for infection'

PH37: Expert paper 4: 'Primary care tuberculosis survey 2010'

PH37: Expert paper 5: 'Cohort review in practice'

PH37: Expert paper 7: 'Tuberculosis control, specifically among hard to reach groups in Rotterdam'

PH37: Expert paper 9: 'Health MOT in a hostel'.

PH37: Expert paper 10 'TB in a London prison'

PH37: Expert paper 11: 'The importance of housing homeless people with tuberculosis'.

PH37: Expert paper 17: 'Nurse led triage'.

PH37: Expert paper 18: 'Nurse led service – Birmingham'.

PH37: Expert paper 21: 'Screening for tuberculosis and HIV in primary care'.

See appendixG for the expert papers summarising the expert testimony.

10.1.4 Fieldwork (PH37)

Fieldwork aimed to test the relevance, usefulness and feasibility of putting the draft recommendations into practice, fieldwork was conducted during the consultation period. The PDG considered the findings when developing the final recommendations..

Fieldwork participants who work in TB services or with hard-to-reach groups were overwhelmingly positive about the recommendations and their potential to help identify and manage TB. Many stated that the guidance was an endorsement for prioritising TB prevention and control. It was viewed as a timely document because of concerns about increasing levels of TB.

Participants felt that the recommendations on planning and funding TB services presented an ideal scenario. As such, they did have some reservations about the likelihood of them being implemented in the current economic climate.

10.1.5 Evidence Statements and Linking Evidence to Recommendations (PH37)

Strategic oversight and commissioning of TB prevention and control activities

Expert testimony on 'Tuberculosis control, specifically among hard to reach groups in Rotterdam' and inference derived from the evidence

Local needs assessment

Inference derived from the evidence

Cohort review

Expert testimony on 'Cohort review in practice'

Commissioning multidisciplinary TB support for hard-to-reach groups

Moderate evidence from three UK studies (one [-] and two [++]) suggested that the complex social and clinical interactions surrounding a patient with TB can be a challenge to participation and adherence, and that outreach TB link workers or social care workers can facilitate coordination of services.

Strong evidence from five studies, two USA RCTs (both [++]) and three before-and-after studies (two USA and one Canada) (two [+]and one [++]) shows that drug misusers who are provided with small monetary incentives are statistically more likely to complete screening compared with no incentives (p = 0.004, [+]; p < 0.001, [+]).

Strong evidence from two USA RCTs (both [++]) found that providing drug misusers with a brief educational programme alone is unlikely to increase the proportion who complete screening compared with no incentives or education (p = 0.786 and p = 0.547).

Moderate evidence from two studies, one USA RCT (++) and one UK before-and-after study (+), suggests that providing monetary incentives increases the uptake of screening (from 23% with no incentive to 62% with a £1.50 incentive and 45% with a £3.00 incentives [+]; and from 53% with no incentive to 84% for $5.00 incentives, p less than .001 [++]).Although the quality of the studies varied, both studies supported the same findings.

Weak evidence from one USA RCT (+) found that adding twice-weekly $5 cash incentives to attend DOPT appointments resulted in statistically greater adherence to treatment completion in the homeless (44%) compared with providing DOPT provided by a peer without incentives (19%; p = 0.02) but that incentives were not significantly more effective than treatment as usual (26%; p 0.11). The clinical significance of these differences is unclear. The generalisability of the study to hard-to-reach groups may be limited as it included participants who lived in apartments and only included those who returned for their TST results within one week.

Moderate evidence from one USA RCT (++) found that drug users with latent TB infection were statistically more likely to complete treatment when provided with incentives (regardless of whether outreach was also provided), compared with DOPT plus outreach without incentives (AOR = 45.5, 95% CI 9.7 to 214.6; p less than 0.0001). However, the confidence intervals are wide, reducing the precision of the results.

Moderate evidence from one USA before-and-after study (+) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with DOT alone (OR = 5.73, 95% CI 2.25 to 14.84) in a population that included over 50% of drug users. The study was limited because DOT was compared with a retrospective cohort of patients.

Moderate evidence from one Spanish before-and-after study (+) found that there was a statistically significant benefit of adding incentives to DOT on treatment completion compared with self-administered therapy (RR = 3.07, 95% CI 2.13 to 4.41) in mixed hard-to-reach groups. The study was limited because DOT was compared with a retrospective cohort of patients and there were significant differences between the cohorts in the two time periods.

Expert testimony on 'The importance of housing homeless people with tuberculosis' and inference derived from the evidence.

Identifying and managing active TB in prisons or immigration removal centres: organisational factors

Expert testimony on 'TB in a London prison' and inference derived from the evidnce.

Contact investigations

Moderate evidence from one case-control study (++, UK) suggests that using mobile X-ray units (MXU) to screen for TB reduced diagnostic delay among hard-to-reach groups in the UK (including the homeless, drug users and prisoners) compared with passive case

detection (adjusted hazard ratio for delay = 0.35, 95% confidence interval [CI] 0.21 to 0.59, p less than 0.0001). People identified as having TB by MXU screening were less likely to be symptomatic on diagnosis compared with those identified by passive case-detection (adjusted odds ratio [OR] 0.35, 95% CI 0.15 to 0.81, p less than 0.001).

Infernce derived from the evidence

Rapid-access TB services

Strong evidence from five studies suggests that hard-to-reach groups (mostly African immigrants) have a lack of confidence in or are concerned about misdiagnoses or delayed diagnosis by healthcare professionals. Groups that mentioned these concerns included:

- Somalis in Sheffield (one [++])
- various vulnerable groups including HIV patients in London (one [-])
- African immigrants in London (two [++])
- Somali and Ethiopian immigrants in Norway (one [+]).

Expert testimony on 'Service user perspectives', 'Nurse led triage', 'Nurse led service – Birmingham' and inference derived from the evidence

Accommodation during treatment

Moderate evidence from three USA studies (all [+]) found that the main characteristic that was shown to be predictive of treatment completion was residing in stable housing before receiving treatment for TB in the homeless and in prisoners. Therefore, participants who live on the streets or in a shelter have poorer adherence to treatment for TB and may need additional support to maintain their adherence with treatment.

Expert testimony on 'The importance of housing homeless people with tuberculosis'. And inference derived from the evidence.

10.1.6 Recommendations

All PH37 recommendations have been incorporated into the updated guideline and adapted as described in relevant sections of the full guideline.

10.2 The organisation and delivery of TB services [2015]

10.2.1 Clinical introduction

A range of TB treatment and prevention services are established in the UK. For example, London features 30 main specialist TB services that provide care for TB patients, alongside a specialist hospital for children with complex disease. An NHS-funded “Find and Treat” programme (including a mobile X-Ray unit) is tasked with engaging with underserved and excluded groups. In addition, five sector-wide clinical networks promote good practice and have in the past supported the local commissioning of TB services (PHAST 2010). However, services vary widely across the UK, both in terms of what is available and how services are configured and delivered.

Update 2015

10.2.2 Evidence review

Service delivery for tuberculosis is an area not in the original guideline that is included in the update using the Centre for Clinical Practice’s interim methods for developing service delivery guidance. This work was undertaken by a service delivery group made up of

members of the Guideline Development Group, plus additional co-opted experts. Recommendations have been drafted by this group on the organisation and management of clinical and public health TB services and subsequently discussed and agreed by the GDG.

A scoping workshop in January 2014 identified the core approach and "*what the best configuration of services to provide high-quality care efficiently and safely*" was selected as the key area of focus for this review. Consideration was given to high level issues such as centralised commissioning and accountability within service delivery. Attention was also given to the different service models that may be required in terms of incidence across areas and regions; and active, latent and drug resistant TB where possible in relation to the main outcomes of interest.

This review has been developed as part of the evidence to inform recommendations on the organisation and delivery of TB services. It takes a mixed method approach to identifying, interrogating and presenting the evidence. It comprises of a systematic literature search to produce three sections of the report:

- Case study profiles of a set of pre-identified cities and countries (UK, New York City, Netherlands, Barcelona and Canada).
- A systematic review of the evidence of the effectiveness of service interventions or models (and aspects of service models) in these case study areas.
- A systematic review of the evidence of the cost effectiveness of service interventions or models (and aspects of service models) in these case study areas.
- A service delivery intervention/model was defined as any service adaptation, such as process changes, change in delivery setting or mode (including staff), and change in structure, accountability or commissioning of a TB service.

Note: The SDG and NICE agreed to use the term 'under-served' to denote the high risk groups previously described as 'hard to reach' in PH37. The definition from this guideline was adopted to describe these groups therefore, where the term under-served is used, this relates to the definition described above in sub-section 13.1 of this chapter.

Update 2015

10.2.2.1 Case Studies (Policy and Practice)

The reports, documents and papers were retrieved and examined from the full search results as described below in the evidence review. Inclusion criteria were that the paper reported on policy, practice or TB services in a case study area.

The first objective of the review was to present case studies which describe TB services in the following places:

- UK
- New York City (NYC)
- Canada
- Barcelona
- the Netherlands.

Studies or papers used in the case studies were not critically appraised due to the more discursive nature of this component of the review. Rather than present effectiveness data, the aim here was to build descriptive pictures of the way that TB services are organised (in themselves and in relation to wider health services where possible) in each case area. Papers identified as being of relevance to case studies were grouped by location. Due to the large volume of information available for this section, much of which overlapped, extraction was not undertaken for individual papers. Instead, for each location, a case study extraction sheet was prepared, focusing on audit questions/themes of relevance to the case studies including notification rates and population patterns in TB cases, governance, legislation and accountability, financing and cost of healthcare and TB services, staffing and settings related

to TB, and a summary of the TB service delivery model for each case. See appendix G7 chapter 3 for detailed case study information.

The case studies provide an overview for case study areas over the last 10-20 years, and where possible, information on sub-populations that are at increased risk for TB, and the national, regional, and local strategic TB priorities. They also include background information and overviews of their service delivery model, specialist staff and settings relevant to tuberculosis in each jurisdiction.

Overall, the case study profiles show that all of the included areas (UK and non-UK) have similar high risk population groups including foreign born people, people living with HIV, people who misuse substances, homeless people and prisoners (with the addition of the indigenous population in Canada). There are also broadly similar priorities and policy direction, for example active case finding, targeting high risk groups, surveillance (including strain typing), improving treatment completion including enhanced case management and DOT, although the targeting and accountability for each element may differ.

The findings from the case studies are summarised below, see the case study chapter in the full service delivery review in appendix G7 for further details and in-depth descriptions of the case study areas.

10.2.2.28 Literature review

The second objective of the review was focused on identifying effective approaches to TB services in the case study areas, in relation to three key outcomes:

- reducing diagnostic delay for TB
- improving TB contract tracing
- improving TB treatment completion.

For this review, papers were identified from a number of databases (Embase via OVID, MEDLINE in Process via OVID, MEDLINE via OVID, PsycINFO via OVID, Health Management Information Consortium (HMIC) via OVID, Social Policy and Practice (SPP) via OVID, Applied Social Sciences Index and Abstracts (ASSIA) via ProQuest, Cumulative Index to Nursing and Allied Health (CINHAL) via HDAS, Cochrane Central, Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluations Database (NHS EED)

In addition the following non-database sources were used

- (African Health Forum via http://www.africanhealthforum.org.uk/index.htm,
- Agency for Health Care Research and Quality via http://www.ahrq.gov/ ,
- Audit Commission via http://www.audit-commission.gov.uk ,
- Australian Clinical Practice Guidelines Portal via http://www.clinicalguidelines.gov.au/,
- Black Health Agency via http://www.thebha.org.uk,
- British Infection Association via http://www.britishinfection.org/drupal/,
- British Society for Antimicrobial Chemotherapy via http://bsac.org.uk,
- British Thoracic Society via http://www.brit-thoracic.org.uk/,
- Campbell Collaboration via http://www.campbellcollaboration.org/,
- Centers for Disease Control and Prevention resources on TB via http://www.cdc.gov/tb/,
- Chartered Institute of Environmental Health via http://www.cieh.org/
- Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register,
- Department of Health via http://www.gov.uk

- Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/,
- European Centre of Disease Prevention and Control via http://www.ecdc.europa.eu,
- Find TB Resources via http://www.findtbresources.org/,
- Guidelines & Audit Implementation Network via http://www.gain-ni.org/,
- Health & Social Care Information Centre via http://www.hscic.gov.uk/ ,
- Health Protection Scotland via http://www.hps.scot.nhs.uk/,
- Health Quality Improvement Partnership via http://www.hqip.org.uk,
- Healthcare Quality Improvement Partnership via http://www.hqip.org.uk/,
- Infection Prevention Society via http://www.ips.uk.net, Institute for Clinical Systems Improvement via https://www.icsi.org,
- KNCV Tuberculosis Foundation via http://www.kncvtbc.org
- Local Government Association via http://www.local.gov.uk/,
- McMaster University Health Evidence via http://www.healthevidence.org/
- National Audit Office via http://www.nao.org.uk/
- National Guideline Clearinghouse via http://www.guideline.gov/
- New York City Department of Health and Mental Health via http://www.nyc.gov/html/doh/html/diseases/tb.shtml
- NHS England via http://www.england.nhs.uk/
- NHS Health Scotland via http://www.healthscotland.com/resources/publications/search-result.aspx,
- NICE via http://www.nice.org.uk/
- NICE Evidence Search https://www.evidence.nhs.uk/
- NIHR Health Services & Delivery Research Programme via NIHR Service Delivery and Organisation programme
- Nuffield Trust via http://www.nuffieldtrust.org.uk/
- OpenGrey via http://www.opengrey.eu/
- Public Health Agency of Canada via http://www.phac-aspc.gc.ca/index-eng.php
- Public Health England via https://www.gov.uk/government/organisations/public-health-england
- Public Health Observatory via http://www.apho.org.uk/
- Public Health Wales via http://www.publichealthwales.wales.nhs.uk/
- Quality, Innovation, Productivity and Prevention via http://www.evidence.nhs.uk/qipp
- Race Equality Foundation via http://www.raceequalityfoundation.org.uk
- Royal College of Nursing via https://www.rcn.org.uk/
- Royal College of Physicians via http://www.rcplondon.ac.uk/
- South Asian Health Foundation via http://www.sahf.org.uk
- Stop TB UK via http://www.stoptbuk.org/
- Target Tuberculosis via http://www.targettb.org.uk/
- TB Alert via http://www.tbalert.org/ and http://www.thetruthabouttb.org/
- Turning Research Into Practice via http://www.tripdatabase.com/
- World Health Organization via http://www.who.int/en/

Included studies screened in as relevant from the initial search were used to support supplementary searching in three ways:

- Backwards reference harvesting: studies will be extracted from the bibliographies of the relevant papers if they are relevant to the scope. Relevant to the scope means TB or tuberculosis is in the title
- Forwards citation searching: the Science Citation Index and the Social Science Citation Index via Web of Science (http://apps.webofknowledge.com) will be used to look for later papers citing the references of interest. All citations will be added to Reference Manager
- Related item searching using PubMed via http://www.ncbi.nlm.nih.gov/pubmed/

If there are 1-100 references they will all be downloaded into Reference Manager if they are relevant to the scope. If there are 101 or more references they will be sorted by relevance and then the first 100 will be downloaded into Reference Manager, if they are relevant to the scope.

Studies were excluded if:

- The population studied was not one of the case study areas.
- The population did not include people diagnosed with active or latent TB, or people identified as at increased risk of TB (i.e. contacts).
- The paper did not include an intervention that could be classified as service delivery according to our definition that is: a service adaptation, such as process changes, change in delivery setting or mode (including staff), change in structure, accountability or commissioning of a TB service.
- The outcomes were not a change in incidence/prevalence rates or time to diagnosis, contact tracing/screening opportunities/transmission rates or treatment completion rates.

From a database of 5377 unique records, 470 full-text papers were assessed (supplementary searching identified a further 86 unique records assessed all excluded) and 34 papers describing 30 primary studies met the inclusion criteria; of these 2 studies were rated high quality (++), 15 moderate (+) and 13 low (–).

Due to the variety of study designs included in this review there was no single critical appraisal tool that could be used across all of the study designs.

Studies that used an audit design, national/regional/local reports or evaluation, or a cross-sectional design were critically appraised using the appropriate checklist from the NICE Interim methods guide for developing service guidance.

The findings from the effectiveness review chapter are summarised in the section below also see the full review for further detail in appendix G7 including full extraction tables and detailed critical appraisals of the literature.

10.2.2.3 Health economics

The third objective was to identify cost-effective approaches to TB services in the case study areas, with any estimates of cost-effectiveness or cost-impact, in relation to three key outcomes:

- reducing diagnostic delay for TB
- improving TB contract tracing
- improving TB treatment completion.

From a database of 5377 unique records, 470 full-text papers were assessed (supplementary searching resulted in 14 additional unique records being assessed - all excluded). Four papers describing 4 primary studies met the inclusion criteria. Of those included only 1 was a full economic evaluation the other 3 were cost impact studies; following critical appraisal 1 study was graded as having minor limitations (++) high quality, 2 studies as having moderate limitations (+) medium quality, and 1 study as having major

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limitations (–) low quality. The critical appraisal of each study is summarised and discussed in detail in the full review (see appendix G7 Chapter 5 economic review).

Trials were excluded if they did not include any economic analysis, i.e. simple costing studies that did not consider costs and associated outcomes.

The findings from the cost effectiveness review chapter are summarised in the section below; also see appendix G7 for detailed extraction tables summarising all cost effectiveness evidence idetfied and critically appraised.

10.2.2.4 Expert testimony

'Colloquial evidence' can complement the scientific evidence or provide missing information on context. It may come from expert testimony, from members of the advisory committees, or from stakeholder comments. It includes evidence about values (including political judgement), practical considerations (resources, professional experience or expertise and habits or traditions) and the interests of specific groups (views of lobbyists and pressure groups).

The GDG received testimony from a number of experts (lay and professional) in the field on a number of topics:

- Practice - Emergency departments (Expert paper 1)
- Rurality and Service Delivery (Expert paper 2)
- North West TB Network: Paediatric TB specialism and a Hub & Spoke delivery model (Expert paper 3)
- Practice - the Leicester experience including rapid radiology referral model (Expert paper 4)
- Cancer networks (Expert paper 5)
- Practice - the Birmingham experience (Expert paper 6)
- Contact Tracing – incident investigation process in congregate settings (Expert paper 7)
- Practice – Experience of people who use TB services (Expert papers 8 a&b)
- Accommodation, Housing and TB (Expert paper 9)
- MDR-TB networks/access to specialist advice (National Advisory Service) (Expert paper 10)
- Policy Update – National TB strategy and TB Control Boards (Expert paper 11)
- TB and HIV collaborative commissioning (Expert paper 12)

The expert papers can be found in appendix G7 (EP1-12)

10.2.2.5 Evidence statements

10.2.2.5.1 Case studies (Policy and Practice)

Service delivery and commissioning

The non-UK case studies organise the provision and delivery of TB services in different ways: NYC, Barcelona and the Netherlands all take a centralised approach, and although the lines of accountability may differ a centralised approach appears to help ensure clear responsibility for different elements of the service. In NYC, one body (the BTBC) is responsible for the whole system (NYC-DOHMH, 2013). In Barcelona the system is led by the Public Health Service with public health nurses acting as the hub of the system supported by community health workers in high risk community settings and clinical unit

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nurse managers in the hospital sector (Cayla and Orcau, 2011). Similarly in the Netherlands MHS:GGD-NL specialist doctors, public health nurses and medical assistants have responsibility for providing diagnosis and treatment in the community in particular in those with complex social needs, whilst hospitals provide treatment for more clinically complex cases such as MDR-TB. The Canadian approach is perhaps more similar to the UK, with a mixture of national support and guidance from the national Public Health Agency with more regional decision making (territory or province) on how services are delivered. This appears to result in variation in service delivery, for example mobile clinics in Saskatchewan target a high risk indigenous population, but other areas with high risk groups do not provide this service (Government of Saskatchewan, 2012).

Finance

Financial input appears to differ markedly with over $40,000 US dollars per notified case committed to TB in the Netherlands and Canada, $24,000 per case in NYC based on 2012 data to around $12,000 per case in London based on 2009 data, we were unable to identify a national picture for TB funding in the UK or funding data for Barcelona (WHO 'country profiles', 2013; Hayward et al, 2010; Menzies et al, 2008).

Legislation

There is a wide range of legislative mechanisms and support for TB prevention and control in the case study areas, including pre-entry screening for immigrants and court ordered detention and treatment in NYC and Canada, and the recent launch of a pre-entry system (PHE, 2014d) and the power to detain and isolate but not treat non-compliant patients in the UK (Ohkado, 2005). The Netherlands take a preventative rather than enforcement approach with sanctions for screening immigrants and compulsory medical examination, but no detainment or enforced treatment. Barcelona had no legislative control measures (Coker et al, 2007, Paolo, 2004; NYC-DOHMH, 2013).

Contact Tracing

All areas included in this review deliver contact tracing using the same method (stone in the pond/concentric circle), with variation found in the staff who delivered it. In Barcelona community health workers recruited as 'peers' of the target group are involved in delivery of contact tracing. In the Netherlands, medical assistants support delivery of contact tracing and in NYC public health assistants deliver contact tracing: This may contribute to variations in the effectiveness of the contact tracing activity (see Effectiveness review). It may also impact on the capacity of specialist public health nurses to deliver other elements of services such as DOT or case reviews, where non-clinical staff take on specific tasks and free up clinical time for other activities (Cayla and Orcau, 2011; Ospina, 2012; Boar and de Vries, 2012).

Targeting high risk groups

All case study places actively target high risk groups, although the approaches used differ. Pre-entry screening is well established in NYC and Canada and has been very recently introduced to the UK. NYC, Rotterdam and London also make use of outreach and mobile X-ray units to diagnose hard to reach groups such as the homeless (de Vries et al, 2007 and 2014; Hayward et al, 2010). However, it is not clear whether MXU outreach activities occur across the Netherlands or only in Rotterdam. Furthermore, in the UK this aspect of the service is only widely used in London (de Vries et al, 2007 and 2014; Hayward et al, 2010). Similarly, mobile outreach clinics being delivered in Northern territories in Saskatchewan (Canada) to high-risk indigenous communities are not available in other areas (Government of Saskatchewan, 2012).

Treatment completion

DOT is a core element of service provision to improve adherence and treatment completion in all case study areas, in particular in relation to vulnerable groups or those at risk of non-adherence. However, the availability of DOT appears to differ markedly. In NYC DOT is a core element of the TB service, and many studies have concluded that consistent use of DOT is responsible for much of the decline in TB over recent years (NYC-DOHMH, 2002). In 2012 it formed the basis of the majority of treatment (487 of 651 cases ~ 75%) and is considered the standard of care. In NYC 94% of cases completed treatment within 12 months during this time (NYC-DOHMH, 2013). In Canada, DOT is recommended as the minimum level of support for patients with risk factors for non-adherence (Pan Canadian Public Health network, 2012), although the levels of delivery of DOT are unknown. In Barcelona again the incorporation of DOT into methadone programmes has been credited with the dramatic decline of TB in people who inject drugs (Cayla and Orcau, 2011). UK data on the provision of DOT is only partially available: between 1.7 and 32% of cases received DOT in London and 0% in Bradford (Bothamley et al, 2011). Given the epidemiological profile of TB in the UK, it is likely that far fewer people were offered DOT than would benefit from it. However without data on the proportion of cases that had a risk assessment and were subsequently offered or provided with DOT it is difficult to draw further conclusions.

Staffing

Staffing ratios of nurses (or other staff) differ across the case study areas from 1:12 in NYC; 1:18 in the Netherlands and 1:35-45 in Barcelona. There are no UK data available to provide a national picture of TB staff:case ratio (Boer and de Vries, 2011; Bothamley, 2011; Cayla and Orcau, 2011). It should also be noted that in the Netherlands medical assistants support public health nurses to deliver case management including DOT and contact tracing in people with complex needs in community based clinics. In Barcelona Community Health Workers support contact tracing in culturally similar high-risk immigrant groups (Ospina et al, 2012). In NYC trained Public Health Assistants are responsible for most case management including DOT, active case finding and contact tracing activities as well as providing formal case review as part of the cohort review process. These support workers are likely to offset the workload of specialist TB nurses in these areas, freeing up clinical time for other duties. In the UK these activities are almost exclusively provided by specialist TB nurses.

Surveillance

Surveillance is consistently prioritised as an important element of service delivery approaches at a national level with national systems for enhanced surveillance and a mandate to report all notified cases in all case study areas. Surveillance is overseen by a national agency in all cases and includes genotyping/DNA fingerprinting as standard. It should be noted reliance on surveillance to support service delivery in Barcelona significantly predates the recent National Plan highlighting the need for a national surveillance system (Cayla and Orcau, 2011).

Cohort Review

NYC and the UK are both reported to use Cohort Review as a way to systematically review the management of every case of TB on the basis of treatment completion, contact investigation and case management process (Bothamley, 2011; Munsiff et al, 2006). Case managers are responsible for presenting the review of their cohort, this process is considered one of the most important approaches to programme evaluation, service improvement and ensuring accountability in NYC (Munsiff et al, 2006). Whilst a number of cities in the UK cited delivery of cohort review (London, Manchester, Leeds and Leicester), it is not clear how systematic this approach is across the UK (Bothamley, 2011).

10.2.2.5.21 Literature review

Cohort review can improve contact tracing in TB patients (ES1)

Moderate quality evidence from one London UK study1 (+) that cohort review can increase contact tracing of at least one contact identified (86% v 77%; p<0.001), compared with before cohort review was implemented. There was no difference in treatment completion (86% v 87%; p=0.6). Other outcomes, such as increased DOT refusal (30% v 10%; p=0.001) were identified as something to address and monitor in future cohort review. Overall, the process was seen as identifying problems and allowing whole system improvement.

There is moderate evidence from one NYC study2 (+) that continuous cohort review can increase contact tracing over time (at least 90% of patients with appropriate contact investigation: 2004: 95.3% v 1999: 90.5%). Treatment completion rates were similar (86.5% v 85.7%), while treatment success was slightly lower over time (2004: 81% v 1999: 83%). Again a large benefit of the process was seen as identifying problems that could then be addressed.

Applicability: The evidence is directly applicable to TB service delivery in the UK. This is because there are no obvious differences in the delivery of cohort review in the included studies compared to how it could be delivered in the UK.

Nurse led service to improve treatment completion in TB patients and reduce costs (ES2)

Moderate quality evidence from one Bristol UK study1 (+) found that a community based nurse-led service can increase treatment completion rates compared with previous monthly hospital based clinics and cases notified to the Health Protection Agency (94% v 84 v 55%%; p<0.0001). Other outcomes, such as assessment for DOT were also improved, compared with previous monthly clinics (92% v 5%; p<0.0001). The nurse-led service was estimated to save £27,872 per year compared to monthly clinics, due to replacing 268 reviews (£104 each).

The evidence is directly applicable to TB service delivery in the UK. This is because there are no obvious differences in the delivery of a nurse-led service in the included study compared to how it could be delivered in the UK.

DNA surveillance of TB cases can support conventional contact tracing (ES3)

Moderate quality evidence from one Netherlands study1 (+) found that DNA surveillance can support conventional contact tracing by increasing epidemiological links based on documented exposure (35% increase; p<0.001), although only 1% of contact investigations were extended. It was seen as being particularly useful training mechanism for inexperienced TB nurses, a method of monitoring the effects of new control policies, and enabling institutional deficiencies to be detected.

The evidence is partially applicable to TB service delivery in the UK. This is because this study was conducted in the Netherlands which may have different contact tracing policies from the UK, which means that the expected benefits of DNA surveillance in the UK could be different.

Educational outreach and incentives to GPs can increase TB screening and diagnosis of TB in people presenting at primary care (ES4)

Moderate quality evidence from one London UK study1 (++) found that education outreach visits by specialist TB nurses and academic GPs to GP practices, together with practice computer system prompts and a £7 incentive for Tuberculin skin test (TST) administration, can increase the proportion of people screened for TB at registration health check, compared

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with usual practice (57% v 0.4%). This increased the diagnosis of active TB (47% v 34%; OR 1.68, 95% CI 1.05 – 2.68), and latent TB (19% v 9%; OR 3.00, 95% CI 0.98 – 9.20), compared with usual care.

The evidence is directly applicable to TB service delivery in the UK. This is because there are no obvious differences in the delivery of this type of intervention in the included study compared to how it could be delivered in the UK. However, the study may only be applicable to high incidence TB areas; in areas of the UK with a lower incidence of TB, the rates of people presenting with TB in primary care may be much less.

Community health workers can increase contact tracing in immigrant communities (ES5)

Moderate quality evidence from one Barcelona study1 (+) found that community health workers from immigrant communities working alongside public health nurses can improve contact tracing performed in all TB cases (66% v 55%; p<0.001) and performed in smear positive cases (82% v 66%; p<0.001), compared with public health nurses alone.

The evidence is partially applicable to TB service delivery in the UK. This is because the demographics of TB patients and contact tracing policies in the UK may vary from that in Barcelona. The results of the study may be most applicable to areas of the UK where there is a high incidence of TB in people from immigrant communities.

Mobile screening can improve treatment completion and active case finding in under-served people (ES6)

Strong quality evidence from two studies (London UK (++),1 Netherlands (+)2) found that a community based mobile radiography unit can increase active case finding by between 23-30% in hard to reach groups in an urban setting, compared with passive case finding/before mobile screening was introduced.

The UK study (++) provides moderate evidence that when a mobile radiography unit is combined with case holding and support it can be used to improve treatment completion (54.6% v 46.2% in first year of treatment), compared with passive case finding. The UK study (++) also provides moderate evidence that the service can be cost effective, with an ICER of less than £10,000 per QALY.

The evidence is directly applicable to TB service delivery in the UK. This is because there are no obvious differences in the delivery of mobile screening in the included studies compared to how it could be delivered in the UK. However, the results of the study may be most applicable to areas of the UK where there is a high incidence of TB in hard to reach groups.

Peer educators can increase TB screening in hard to reach groups (ES7)

Weak quality evidence from one London UK study1 (–) found that peer educators working alongside TB clinics and mobile screening units can increase TB screening uptake compared with before peer educators were introduced (75% v 44%).

The evidence is partially applicable to TB service delivery in the UK. However, the results may be most applicable to areas of the UK where there is a high incidence of TB in hard to reach people.

Rapid access referral triggered by radiology coding of abnormal chest x-rays can reduce diagnostic delay in TB patients (ES8)

Moderate quality evidence from one Leicester UK study1 (+) found that rapid access referral triggered by radiology coding of abnormal chest X-rays statistically significantly reduces the

duration of symptoms in non-pulmonary TB (78.4 v 122.1 days; p=0.03) and smear positive pulmonary TB (60.2 v 95.9 days; p=0.03), compared with other diagnostic pathways. There was a non-significant reduction in the duration of symptoms in smear negative pulmonary TB (80.4 v 100.1 days; p>0.05). There was a non-significant lower rate of contact tracing with radiology referral compared with other diagnostic pathways (mean number of contacts 4.57 v 4.91; p>0.05).

The evidence is directly applicable to TB service delivery in the UK. However, the results may be most applicable to areas of the UK where there is a high incidence of TB or large proportions of the population are at increased risk

Comprehensive MDR-TB control programme can improve treatment completion in MDR-TB patients (ES9)

Moderate quality evidence from one NYC study1 (+) found that a comprehensive MDR-TB control programme can improve treatment completion in MDR-TB patients (44% v 12%; p<0.001) and reduce death prior to treatment completion (39% v 69%; p<0.001, compared with outcomes reported at the start of the programme.

The evidence is partially applicable to TB service delivery in the UK. This is because the demographics and management of MDR-TB patients in the UK may vary from that in NYC.

Involuntary detention can improve treatment completion in non-compliant TB patients (ES10)

Moderate evidence from one NYC study1 (+) found that involuntary detention followed by court-ordered DOT improves treatment completion in non-compliant patients compared with standard DOT (95% v 89%).

The evidence is partially applicable to TB service delivery in the UK. This is because the demographics and management of non-compliant TB patients in the UK may vary from that in NYC.

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10.2.2.6 Health economics

Testing for latent TB in an HIV service can increase diagnosis of latent TB in HIV patients (ES11)

Weak evidence from one Leeds UK study1 (–) found that testing for latent TB in an HIV clinic can improve rates of identification of cases of latent TB (24/101 people tested, of which 4 tests were abnormal). The cost was estimated to be £12,760-£23,720 per year, compared with £14,776 to £53,194 for treating active cases.

The evidence is directly applicable to TB service delivery in the UK. This is because the demographics of HIV-TB patients and HIV-TB screening policies in this study are likely to be the same as in the rest of the UK.

10.2.3 Strategic oversight and commissioning of TB prevention and control activities

10.2.3.1 Evidence to recommendations

Relative value of different outcomes	The group considered that reducing delays in diagnosis and increasing the number of patients who complete treatment are the priority outcomes for strategic oversight and commissioning of TB prevention and control services. These outcomes were considered highest priority, because achieving these would lead to other important outcomes considered, such as a reduction in risk

	and rates of transmission of TB and reduction in both morbidity and mortality associated with TB.
Trade-off between benefits and harms	The benefits of implementing strategic oversight and commissioning of TB prevention and control activities include the ability to reduce variation in practice in terms of diagnosis, treatment and monitoring of those with TB and ensuring that there are clear communication channels across different services (NHS, Social Care and Public Health), infection control protocols that are fit for purpose and other activities. In other healthcare, for example with cancer networks, strategic oversight has enabled the services to be more responsive to current events and has made it easier to share best practice and continued learning. Harms associated can include the risk of over management (where decisions are made by managers not by clinical staff) and of losing local knowledge and experience which may impact on local relationships across services especially with 'under-served' groups. The committee noted the lack of empirical and outcome evidence from evaluations of national, regional or local service models for organising, commissioning and delivering TB services. However, they agreed that the case study review showed that centralised approaches to commissioning and service organisation and delivery at regional or city wide level are associated with marked declines in TB incidence and prevalence. In particular key factors they considered were associated with successful TB services were: political will, leadership, cohesion, ownership and an emphasis on tackling problems among under-served groups. It was noted that the level of staff resources devoted to TB control in New York, Barcelona and the Netherlands was substantially greater per case than in London, the committee agreed this was likely to have an impact on the effectiveness of the service in relation to the service outcomes above however, there was no effectiveness evidence to support this conclusion.
Trade-off between net health benefits and resource use	There have been no changes to the intent or meaning of recommendations incorporated from PH37. Whilst they have been extrapolated from under-served groups to the whole population in some cases and adapted to fit to the current service commissioning and delivery landscape following the Health and Social Care Act such as organisational names and recognition of CCGs and their commissioning responsibilities along with the movement of Public Health into local government and the creation of health and wellbeing boards the adaptations are not considered to have any financial impact as activities already recommended by NICE in PH37 have not changed. The only addition is due to ring fenced money being made available in the NHS to set up TB control boards. As this is the only new cost implication, the committee did not therefore place an emphasis on the trade-off between benefits and resource use in relation to including a new recommendation on the establishment of TB control boards as this was being pump primed by new money they did however make a research recommendation to encourage evaluation of the outcomes of these new bodies.
Quality of evidence	No high quality comparative evidence was found evaluating service change at a strategic level or evaluating a particular strategic or collaborative service model in the UK or wider, a variety of evidence from case studies and expert testimony was used and all were considered low quality. Whilst the expert testimony was considered low quality based on the evidence hierarchy it was considered applicable by the committee to decision making to support recommendation development as it was all from the UK. Applicability of the evidence from case studies varies, as they have different systems or organisational arrangements for delivery of TB services as well as different geographical areas for delivery ranging from moderate sized

	metropolitan city (Barcelona) to a much larger metropolitan area (NYC) and a national example of mixed urban and rural delivery (Netherlands). The committee believe that the examples reviewed are applicable to different areas of England and therefore map across effectively to control board areas that are likely to exist in the UK. Whilst the way in which centralisation is approached may differ, the committee considered the co-ordinating aspect with specific roles and responsibilities for those centralised services and structures to be a core element of the positive outcomes observed in the case study areas. These functions roles and responsibilities are an integral element of overseeing the commissioning of TB prevention and control activities and there was no reason that form and function could not be transferred to the UK. Therefore the evidence reviewed in the case studies was considered applicable to the UK. However, given the descriptive nature of the evidence in the case studies there remained uncertainty in the direct impact of the strategic oversight and commissioning on TB prevention and control outcomes. The group discussed if sufficient evidence was available to make stronger recommendations on the commissioning footprint for TB services. It concluded that although evidence on a metropolitan city level was available this was insufficient to make that strong recommendations and considered that decision should rest with NHS England and the Department of Health. Given the limitations of the evidence available, the recommendations were reached on the basis of expert consensus of the committee.
Other considerations	The aim of the recommendations are to promote an integrated approach centred around inter-professional collaboration, leadership and commissioning footprints. New recommendations or changes to PH37 recommendations are inferred from the evidence provided in the case studies and expert testimony through a consensus approach underpinned by their expertise and experience. <u>Strategic Direction</u> The group discussed the importance of recognising and aligning with the National Strategy and any recommendations should be implementable within the context of the strategy. <u>Collaboration</u> The group agreed that collaborative commissioning 'should be considered' as they felt this is needed in some geographical areas; particularly where there are few cases and thus, expertise at a CCG level may be lacking and in such areas it would make sense to cross geographical boundaries. It was highlighted that as TB is a communicable disease with considerable public health risk there is no justification for not providing a service even if it is not a local priority thus collaborative approaches would also help to support the viability of services in low incidence/prevalence areas. This would aid management of socially and clinically complex cases as working and commissioning across traditional boundaries should help to manage the risks of ensuring consistent provision that meets the needs of all affected people. Any level of collaboratively commissioning was deemed appropriate (for example Warwickshire model-EP2 and North-West network model EP-3) as all levels offered the capacity to share resource and expertise. Additionally the testimony based on Birmingham practice (EP6) highlighted that CCG collaboration was a good approach to preventing fragmentation of commissioning that came with the NHS reforms and which works against public health problems that require joined up solutions due to the differences in needs across a whole population when working across large geographical

areas.

Leadership

The group adapted PH37 recommendations to account for the current and recently launched configuration and structures within services such that TB control boards and their remit take an over-arching role in supporting the development of local commissioning models but that the commissioners such as CCGs and local government were at the forefront of decision making. They also highlighted the need to consider TB prevention and control services from the perspective of an 'end to end' pathway, that is from prevention to cure and follow-up where relevant. This includes accounting for the perspectives of the different providers of the service considered responsible for delivery so that a comprehensive and co-ordinated clinical and public health service is developed and commissioned where possible jointly across the agreed geographical footprint.

The group discussed local leadership and responsibility, whilst a local Director of Public Health or public health consultant should be responsible for working with the CCG as the communicable disease expert, it was crucial to have leadership from the CCG to sponsor the programme of work as the CCG holds the 'purse strings', and agreed 'executive director' would be the appropriate person to take action.

- These points were further debated by the GDG when reviewing the recommendations drafted by the SDG. They agreed overall with the need for both local and broader leadership and decided to make this clear by having two separate recommendations at a TB control board level and then at a local level, describing the broad range of people needed on the board and the leadership needed from relevant CCGs by an executive director, who will have the leverage to drive implementation.

Other:

The group added 'free treatment' as an important aspect of 'case management/DOT' and felt this should be clarified in the bullet point outlining some core aspects of TB prevention and control programmes. This list was further updated to remove duplication of actions that would be the remit and functions of TB control boards, these aspects are covered in the new section on Developing the TB control programme.

The group also discussed the role of the voluntary sector in service commissioning, in particular when thinking about working with other groups and services and agreed they needed including explicitly as an actor in the recommendations, particularly when considering their evolving role as a commissioner and provider in the current landscape which could change rapidly, they highlighted examples they already knew of where they acted as commissioners of NHS services for example Turning Point and the El-Alia Centre, and agreed this is likely to expand in time.

Expert testimony (EP12), showed in practice that on occasion clinicians from one specialism (in this instance HIV) may identify and treat TB within their role as a person's lead clinician for HIV but they did not always seek advice from TB specialists as recommended elsewhere in this guideline.

- It was thought by the GDG that recommending joint clinics and/or training may overcome this issue and may also aid in efficiency of service provision particularly if joint clinics occurred. This may also reduce the burden on the person with TB when attending for multiple treatments on a regular basis. It was noted there may be other synergies between services and interventions to improve the identification and management of TB among particular groups that could also be used to tackle other diseases that disproportionately

affect people with TB for example co-location with drug services as described in the case studies. They felt that an alternative approach would have been to make recommendations on a range of common conditions but felt they had not received sufficient evidence to do this for services other than TB-HIV.

Expert testimony (EP8) about lack of information and support negatively impacting on the patient experience also prompted the committee to make a new recommendation for all services to consider providing information and support irrespective of a person being considered under-served.

There were a number of other considerations the committee debated when adapting the incorporated recommendations:

- Population mobility in particular under-served groups often cross organisational boundaries of different services particularly locally commissioned services, taking a broader perspective may mitigate this risk.
- Within one locality, there may be insufficient number of socially complex TB cases to merit the commissioning of specialised services collaborative commissioning may overcome this.

A wide range of clinical and public health activities and practitioners are involved requiring appropriate communication channels such as TB control boards and partnership approaches to be established.

10.2.41 Recommendations

181. Public Health England, in partnership with NHS England, should take responsibility for national oversight of TB prevention and control activities. This includes setting up TB control boards (see Developing the TB prevention and control programme). [2012, amended 2015]

182. Public Health England and NHS England should work together to establish control boards in agreed geographical areas and employ appropriate staff (see recommendation on TB control board staff). [new 2015]

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183. Clinical commissioning groups and local authority public health teams working in partnership with Public Health England and NHS England should consider collaborative commissioning arrangements through TB control boards. This could, for example, include working with 1 or more clinical commissioning groups to cover a major metropolitan district, region or TB control board area taking into account:

- local TB incidence
- local at-risk populations and their movements across different geographical areas
- existing service configurations for organisations involved in TB prevention and control
- the need to share services, such as mobile X-ray facilities, across different geographical areas. **[2012, amended 2015]**

184. TB control boards should develop TB prevention and control programmes working with commissioners, Public Health England and NHS England. The board could include clinical, commissioning (from clinical commissioning groups, local government and the voluntary sector) and public health leaders and people with TB or groups who advocate on their behalf from across the control board area. This may include identifying a lead clinical commissioning group, which could be led by an executive director of that commissioning group working with the board.

Develop feedback mechanisms between local commissioning groups and the TB control board. [new 2015]

185. An executive director of local commissioning groups working with the local director of public health or another nominated public health consultant should lead implementation of the programme in their locality. The lead should ensure a comprehensive prevention and control programme is commissioned to support the level of need (see needs assessment recommendations) and that they work with the control board regularly. [2012, amended 2015]

186. Working together through TB control boards and local networks, commissioners, local government and Public Health England should ensure TB prevention and control programmes set up multidisciplinary TB teams to provide all TB services (see recommendations on commissioning multi-discilinary TB teams). They should ensure that local strategy and service commissioning focuses on an end-to-end pathway. [2012, amended 2015]

187. Working together through TB control boards, commissioners and Public Health England should ensure the TB prevention and control programme is informed by relevant NICE guidance and developed in collaboration with clinical services. It should also be informed by the standard minimum data set collected through local needs assessment and service audit (see needs assessment). [2012, amended 2015]

188. Working together through TB control boards, commissioners and Public Health England should ensure the TB prevention and control programme targets all ages, including children, and covers all aspects of TB prevention and control (see Developing the TB prevention and control programme), including but not limited to:

- active case finding (contact investigations and identifying latent TB in high-risk groups)
- awareness-raising activities
- standard and enhanced case management (including providing directly observed therapy and free treatment)
- finding those lost to follow-up and encouraging them back into treatment
- incident and outbreak control
- monitoring, evaluating and gathering surveillance and outcome data. **[2012, amended 2015]**

189. Working together through TB control boards, commissioners, Public Health England and the voluntary sector should ensure TB prevention and control programmes take account of the need to work with other programmes targeting specific high-risk groups, such as those who are under-served. Examples include programmes focused on the health of asylum seekers and refugees, under-served children, homelessness and housing, offenders and substance misusers. [2012, amended 2015]

190. Working together through TB control boards, commissioners, Public Health England, the voluntary sector, clinical teams and managers should consider whether TB prevention and control programmes need to develop integrated TB/HIV services. Such services could include joint clinics and training opportunities with medical, nursing and psychosocial input from both TB and HIV specialists. [new 2015]

Update 2015

191. Commissioners should consider offering support and advice to all groups diagnosed with TB irrespective of whether they are under served (see Raising and sustaining awareness of TB). [new 2015]

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10.2.5 Developing the TB control programme

10.2.5.1 Evidence to recommendations

Relative value of different outcomes	The committee agreed that the main outcomes for this set of recommendations are a year-on- year decrease in incidence of TB and prevalence of TB in the UK as described in the TB strategy and this is how success of the TB prevention and control programme and TB control boards would be measured. Achieving the prioritised outcomes for the service delivery work namely reducing delays in diagnosis, improvements in contact tracing and increases in treatment completion would support this outcome and would also lead to other important outcomes considered, such as a reduction in risk and rates of transmission of TB and reduction in both morbidity and mortality associated with TB.
Trade-off between benefits and harms	The benefits of TB control boards were considered to include the capacity to build on the assets that the NHS and the public health system already have in place, to support and strengthen local services in tackling TB (particularly in areas of high incidence), to ensure clear lines of accountability and responsibility, providing national support for local action. This would in turn reduce the harm that TB causes to many individuals and communities. The committee considered the harms associated with not investing in TB control boards being a failure to prevent, diagnose and adequately treat TB cases leading to development of drug resistance, onward transmission and TB outbreaks, including outbreaks of MDR-TB, as well as increased mortality from TB. The committee recognised the benefit of co-ordinated services and considered the unifying aspect envisioned for the control boards (and local networks where applicable) as one of the elements that was of particular importance given the evidence on the way in which centralised organisational aspects for TB prevention and control appeared to be so beneficial in places such as NYC, Barcelona and the Netherlands as indicated by the case study review. However they also recognised they had received no published comparative evidence identifying the most suitable approach to developing a TB control programme or on directly applicable outcomes for TB control boards. The group therefore relied on expert testimony and their expert considerations of how these control boards may support service organisation and delivery in the UK. <u>Coordination of the TB networks</u> They considered the benefits of network co-ordination being further support of the TB control boards efforts in areas where higher levels of local need were identified. It was agreed this need would have to be established by TB control boards working with local service providers. Following expert testimony the group discussed the evidence that showed that lack of support at this level for paediatric commissioning and service delivery for TB had resulted in senior clinicians working extra hours to set up a network leading to not only poor work/life balance but also opportunity costs for other paediatric services (EP3), however, they recognised in this case that a TB control board may have overcome this issue, therefore a network co-ordinator

	would not be required in this instance. The group subsequently noted evidence indicating that having a co-ordinator to enable working across multiple clinical commissioning groups and local authorities was an important element in one area of the UK being able to establish joint working programmes and processes (EP6). In terms of outcomes, the committee heard evidence that the TB co-ordinator was deemed to provide a strong leadership role, which was seen as essential in some areas, although it was too soon for this benefit to be quantified in terms of how it related to TB control. • The GDG concurred with the discussion and conclusions raised, but agreed that in some places in the UK that local network co-ordination may be needed to support implementation to overcome for example complex cross boundary issues. However, they wanted to make it clear that they were not advocating for co-ordinators to be employed everywhere this was likely to be the exception than the rule and should be decided at board level.
Trade-off between net health benefits and resource use	No formal cost effectiveness evaluations of network co-ordination or control boards in TB were identified. **Developing the TB control programme** New funding has been guaranteed to cover the cost impact of the setting up of TB control boards. It was anticipated by the group that TB control board staff are expected to be relatively senior, and therefore the committee thought that TB network co-ordination staff (**if** considered important locally) may not need to be so senior, although this is a decision for local commissioning groups and collaborations depending on their specific needs. One function of the TB control board is evaluating their impact on active and latent TB. It is anticipated monitoring and evaluation work by the commissioners of the boards – (by PHE and NHS England) will determine their cost effectiveness in due course. Recommendations reflect the national strategy content and funding for control boards being provided by PHE and NHS England, no additional recommendations have been made pending evaluation of this aspect of service delivery in due course. <u>Coordination of the TB networks</u> The group heard evidence that TB co-ordinators are employed at a band 8a to 8c depending on the level of seniority required for the post (EP 3/4). It noted evidence that in some areas TB co-ordinators can free up clinician time, but felt this was not enough to off-set costs. On balance, the committee felt that in some areas, particularly if working across multiple clinical commissioning groups, the costs of employing a TB co-ordinator could be justified by the benefits in terms of improved leadership and partnership working. The committee also considered that in some situations a lower band post may be more appropriate, which would reduce the cost impact. They moderated the strength of the recommendations as they had received no cost effectiveness evidence to support strong recommendations in this area.
Quality of evidence	Given the limitations of the evidence available, the recommendations were reached on the basis of expert consensus of the committee. **Developing the TB control programme** The evidence used to support changes to this section and specified recommendations includes both the case study review and Expert papers. Case study applicability varies, but have different systems for delivery of TB services as well as geographical areas for delivery ranging from moderate sized metropolitan city (Barcelona) to a much larger metropolitan area (NYC) and a national example of mixed urban and rural delivery (Netherlands). The committee believe that the examples reviewed are applicable to different areas

	of the country and therefore map across effectively to control board areas that are likely to exist in the UK. Whilst the way in which centralisation is approached may differ, the committee considered the co-ordinating aspect with specific roles and responsibilities for those centralised services and structures to be a core element of the positive outcomes witnessed in the case study areas. These functions roles and responsibilities are an integral element of the TB control boards therefore the evidence reviewed in the case studies was considered applicable to the UK. Relevant testimony and evidence for this section was provided by: ○ EP 11: Policy Update - National TB Strategy. The strategy notes the New York City and the Netherlands practice examples were considered as the basis for development of the strategy along with expert and stakeholder input during the consultation process. The NYC and Netherlands examples have significant crossover with the evidence reviewed formally by the SDG in the service delivery review. ○ Service delivery evidence review (Chapter 3: Case Studies and Summary statement 1 appendix G7 and summary statements above): The non-UK case studies show that three places where epidemiological evidence has shown a significant shift downwards in TB incidence and prevalence of the last 20 years organise the provision and delivery of TB services in different ways. New York City, Barcelona and the Netherlands all take a centralised approach, whilst the lines of accountability may differ by place a centralised approach appears to help ensure clear responsibility for different elements of the service. In NYC, one body (the BTBC) is responsible for the whole system (NYC-DOHMH, 2013). In Barcelona the system is led by the Public Health Service with Public Health Nurses acting as the hub of the system supported by community health workers in high risk community settings and clinical unit nurse managers in the hospital sector (Cayla and Orcau, 2011). Similarly in the Netherlands Municipal Health Services (MHS:GGD-NL) specialist doctors, public health nurses and medical assistants have responsibility for providing diagnosis and treatment in the community in particular in those with complex social needs, whilst hospitals provide treatment for more clinically complex cases such as MDR-TB. In all cases roles and responsibilities are clear and there is a centralised organisational and/or reporting element. This would have been less applicable to the UK given the multiple CCG and other service elements in place since the NHS reorganisation. However, following the recent announcement of additional funding to set-up TB control boards (January 2015), then this aspect of service co-ordination and organisation across the various fragments of the system through a centralised approach with two funding bodies and one taking lead responsibility is transferable. <u>Coordination of the TB networks</u> Overall the quality of the evidence on which co-ordination of TB networks was based is considered low as it is wholly focused on expert testimony which is thought to introduce biases and uncertainties and as such is considered of very low quality in the hierarchy of evidence. Relevant testimony for this section was provided by: ○ EP3: Practice - North West TB Network: Paediatric TB specialism and a Hub & Spoke delivery model ○ EP4: Practice - the Birmingham experience ○ EP6: Practice - the Leicester experience including rapid radiology referral model ○ Cost Impact Analysis: Chapter 8 – TB coordinator see appendix G7 cost impact report for details
Other Considerations	**Developing the TB control programme** The committee discussed the evidence provided by Sarah Anderson. It noted that new ring-fenced funding (£11.5 million) is available to support the

development of the TB control programme by TB control boards, although it also recognised that as yet continued funding had not been confirmed. The group noted the remit and function of TB control boards detailed in the full strategy overseen by the two commissioning bodies for the control boards namely Public Health England (PHE) and NHS England (NHS E). The group agreed that capturing a recommendation on TB control boards before they were functioning had risks. However it also agreed that the service guidance would be out of date immediately and an important aspect of co-ordination of the prevention and control of TB would be missing if they were not captured. Therefore a recommendation was made based on the evidence review, expert testimony (EP11).

The group were keen to emphasise that the control boards will support and complement clinical leadership, not to replace it.

Coordination of the TB networks

In addition the committee noted the importance of systems and service level agreements where multiple commissioners and providers have responsibility for control and treatment. It acknowledged the benefit of networks agreeing roles and responsibilities in managing and governing the system across new and traditional boundaries to reduce not only risk of fragmentation and the risk of diminishing expertise with having multiple clinical settings involved potentially resulting in relatively small numbers of TB cases. This issue was considered important enough to need a dedicated coordinator of the network in some areas.

The group discussed the fact that there is no single organisation charged with the overall responsibility for controlling TB, and no single organisation that has all the necessary levers to do so (EP6). It discussed that this was unlikely to change and did not feel it had the remit or evidence to recommend this should change. Although evidence from the case studies showed that places with a coordinated and in some cases centralised commissioning model had outcomes the United Kingdom would like to replicate (NYC model), this evidence was based on a large metropolitan area and not at a national level so it was difficult for the group to extrapolate this with any certainty. Thus having an individual focussed on developing a strategic coalition involving a large number of players – at local level commissioners, clinicians, local government, Public Health England and the Third Sector was considered a necessity by one testimony provider (EP4). However, the committee did not think this was warranted in most cases.

10.2.61 Recommendations

192. TB control boards should be responsible for developing a TB control programme - based on the national strategy and evidence-based models [new 2015]

193. TB control boards should plan, oversee, support and monitor local TB control, including clinical and public health services and workforce planning [new 2015]

194. TB control board staff should assess services in their area, identify gaps in provision and develop plans to meet these, including:

- undertaking a workforce review to support local or regional commissioning of TB services to meet the needs of their population
- supporting development of appropriate services and pathways to improve access and early diagnosis

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- negotiating arrangements to cover the cost of additional services to address specific gaps in current TB control arrangements. **[new 2015]**

195. TB control boards should ensure cohort review is undertaken at least quarterly (see section 1.8.6), and the results are fed back to local clinical and TB networks. These should be agreed by accountable bodies such as clinical commissioning groups, trust management, regional Public Health England and centre directors and local authority directors of public health as agreed, all of whom should make sure appropriate action is taken. [new 2015]

196. TB control boards should enable full and consistent use of national guidelines including:

- ensuring the needs of all people with TB, particularly under-served populations, are addressed (see sections 1.1.1, 1.1.2, 1.6.3, 1.7, 1.8.1, 1.8.5, 1.8.10, 1.8.11 and recommendations 1.2.1.21–24 and 1.6.2.2–9)
- ensuring contact tracing arrangements are appropriate to the needs of the population (see section 1.6)
- assuring themselves that TB control in low-incidence areas is established and delivered appropriately (see section 1.8.4)
- assuring themselves that multidrug-resistant TB is managed appropriately (see section 1.4.1) and mechanisms are in place to ensure:
  - there is sufficient clinical expertise available to manage cases
  - regional multidrug-resistant TB networks take account of expert advice (see section 1.8.3). [new 2015]

197. TB control boards should develop links and partnerships and establish agreed relationships and lines of accountability between TB control boards and local clinical and TB networks. This includes engaging with other key stakeholders to ensure universal coverage of TB control efforts. [new 2015]

198. TB control boards should collaborate with their local and regional partners. They should agree and establish regular monitoring, surveillance and reporting arrangements with all partners to support needs assessment (see section 1.8.5) and regular audit and evaluation. [new 2015]

199. TB control board staff should, as a minimum, include a control board director and a manager. Their roles and responsibilities should include:

- Establishing the links, partnerships and relationships between all aspects of the control board area within their remit (if necessary across usual geographical commissioning boundaries).
- Developing and supporting adoption and implementation of evidence-based model service specifications for the clinical and public health actions needed to control TB including:
  - improving access and early diagnosis (see sections 1.1.1, 1.1.2 and 1.8.9 and recommendations 1.3.1.28–33.)
  - diagnostics, treatment and care services (see sections 1.2 and 1.3
  - contact investigations and tracing
  - cohort review (see section 1.8.6)
  - vaccination (see section 1.1.3)
  - drug resistance (see section 1.4.1)
  - tackling TB in under-served populations

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- surveillance, monitoring and quality assurance
- workforce development and commissioning (see section 1.8.7 and 1.8.8). [new 2015]

200. TB control boards should ensure there is enough capacity available to them to manage a sudden increase in demand such as:

- TB contact investigations, (such as incidents in congregate settings)
- large scale active case-finding initiatives in under-served groups in the community
- outbreaks in a variety of settings or sites where transmission risk may be high, including but not limited to schools, workplaces, hostels and prisons. [new 2015]

201. To set up, monitor and evaluate a TB control programme, TB control boards will need to:

- agree plans within their partnerships to assess local services against the service specifications
- develop plans and quality standards to secure improvements
- establish quality assurance mechanisms and regular audits including but not limited to cohort review for all aspects of the TB control board partnership plans. **[new 2015]**

Coordination of the TB networks

202. TB control boards should (in collaboration with commissioners) consider the need for a local TB network coordinator, particularly if working across multiple clinical commissioning group areas (see Strategic Oversight recommendation). [new 2015]

203. The coordinator should work in close collaboration with clinicians and all relevant multidisciplinary TB teams to develop the network and be responsible for:

- setting up the network and developing it based on needs, reporting back to the TB control board regularly
- establishing the links, partnerships and relationships across their local network (if necessary across usual geographical commissioning boundaries). **[new 2015]**

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10.2.7 Research recommendations

16. Organisation of TB prevention and control services through TB control boards

Are TB control boards effective and cost effective?

Why this is important

Throughout their discussions, the GDG were aware of the new developments and funding for supporting TB prevention and control efforts in the UK namely the National Strategy and the ring fenced monies being made available to support the national strategy through development of TB Controls Boards across the UK. The organisation of TB prevention and control activities through more regionalised mechanisms such as TB control boards was considered to be a corner stone of improving TB service delivery and reducing variation, improving access to expertise with the potential to impact the time taken to diagnose TB and initiate appropriate treatment, support treatment completion and improve contact tracing

all of which should have downstream impacts on overall morbidity and mortality rates. Quantitative, qualitative and process evaluations of TB control boards using a mixed methods approach to include benchmarking against relevant NICE guideline recommendations and on-going evaluation of surveillance data are recommended.

10.2.87 Regional multidrug resistant TB network

10.2.8.18 Evidence to recommendations

Relative value of different outcomes	The group felt that the key outcome of interest here was to encourage access to and systematic consideration of specialist advice so that effective treatment can begin promptly. MDR-TB requires longer and more complex treatment regimens, which are associated with significantly increased side effects and treatment costs, and poorer outcomes, the committee considered access to expert advice as a means to mitigate these issues.
Trade-off between benefits and harms	The committee agreed that the likely benefits of having expert centres or accessing Multidrug-resistant TB (MDR-TB) specialist advice systematically included reductions in variation in management of MDR-TB which in turn may reduce likelihood of inappropriate regimens being selected with the potential to reduce adverse events and transmission if MDR-TB cases are not diagnosed quickly enough. In particular the committee highlighted that it recognised MDR-TB as relatively low incidence in the UK compared to some other countries, given this low incidence and the recognition by the committee that low case numbers may limit development of clinical expertise it was important to ensure that anyone treating MDR-TB had access to expert advice routes to minimise potential harms. In NYC (case studies, effectiveness review and committee members experience of the system) - all MDR-TB cases are discussed by one reference clinic with an MDR-TB surveillance co-ordinator supporting information exchange via network co-ordinators. This cannot happen readily in the UK as that system is based on a single metropolitan footprint and not a national picture. However, given the current TB networks already in place in the UK the committee considered that it may be beneficial to have regional MDTs and MDR-TB centres of excellence for more complex cases, that could link up through the TB control boards and networks once established. The main action being to steer clinicians to refer/discuss cases with MDR specialists and to access the appropriate advice networks on a systematic basis and for this to be part of the standard operating procedure and reporting for all identified MDR-TB cases.
Trade-off between net health benefits and resource use	The TB advisory service is already in existence the recommendations encourage the use of this service with the likely impact being improved treatment decisions for multi-drug resistant TB which could have large scale cost benefits in the longer term. The committee discussed whether this may have an impact on clinicians availability and agreed the benefits of treating MDR-TB through expert advice including the benefit to the patient of having the correct treatment in a more timely manner would off-set any cost of setting up and attending the regional meetings with knock-on benefits of upskilling clinicians through experiential learning and reducing potential future mis-treatment. The inference of the committee was that incorrect treatment was much more common in the more complex cases such as MDR-TB so getting it right quicker was essential for the patient and for saving future costs..
Quality of evidence	The evidence used to develop this section of recommendations includes direct verbal testimony from identified experts; evidence from the case studies and comparative and non-comparative data in the effectiveness review, no cost

	effectiveness evidence was identified. Applicability of the evidence from case studies and effectiveness review for MDR-TB was limited as this only related only to a larger metropolitan area (NYC). However, there was one non-comparative study from the UK and the expert testimony was also UK focussed therefore directly applicable to UK services. Relevant testimony and evidence for this section was provided by: ○ EP 3: Practice - North West TB Network: Paediatric TB specialism and a Hub & Spoke delivery model ○ EP 10: MDR-TB networks/access to specialist advice (National Advisory Service) ○ EP 11: Policy Update - National TB Strategy. The strategy notes the New York City and the Netherlands practice examples were considered as the basis for development of the strategy along with expert and stakeholder input during the consultation process. The NYC and Netherlands examples have significant crossover with the evidence reviewed formally by the SDG in the service delivery review. ○ Service delivery evidence review (Chapter 4: Effectiveness Review Evidence Statement 9 appendix G7 and evidence statements above - Comprehensive MDR-TB programme can improve treatment completion in MDR-TB patients) ○ Service delivery evidence review (Chapter 4: Effectiveness Review appendix G7): A non-comparative report of the British Thoracic Society MDR-TB Clinical Advice Service/Advisory (Cullen, 2012) was included in the effectiveness review but did not form part of an evidence statement due to the lack of comparator. However, this paper indicated that the MDR-TB Advisory Service increased case discussion by 45% (since its introduction) and confirmed 41/64 cases of MDR-TB and 4/64 cases of XDR-TB. This is directly applicable to the UK and the advisory service referred to in the recommendation. However, as a non-comparative paper Cullen, 2012 was graded as (-) low quality, due to the nature of the study as explained in the service delivery review (see appendix G7) • Given the limitations of the evidence available, the recommendations were reached primarily on the basis of expert consensus of the committee.
Other considerations	The committee discussed the possible fragmentation and variation in services they were aware of and perceived this as problematic and something which may be exacerbated in cases of MDR-TB. In particular the low volume of cases means that care in low incidence areas may not be equal to that in high incidence areas due to lack of specialism. The Group recognised a need for either specialist access points or access to care and advice for everyone, which could be supported by having centres of excellence to help support minimum standards everywhere. Further discussion recognised that establishing centres of excellence may be costly. Quality of care is often contingent on having sufficient numbers of cases to develop and maintain that excellence. The Group recognised that this needed to extend to non-clinical services such as laboratories too. The Committee therefore suggested that as it was concerned with the ability to concentrate services based on numbers and considered that in the case of MDR-TB it is critical there are a minimum number of cases to maintain excellence, that it may be beneficial to approach this on a specialist commissioning basis. However, the Group felt that given the current service configuration this is unlikely they also acknowledged that they did not have strong evidence to base such a recommendation on. Therefore, they focused recommendations on enhancing existing networks. The evidence on paediatric TB services supported this and suggested that in paediatrics this kind of centralised resource is acceptable for TB and other conditions. For example Great Ormond Street and/or the BTS MDR-TB advisory network (or both) are accessed to support appropriate care (EP 3).

10.2.9 Recommendations

204. TB control boards should consider setting up a regional multidisciplinary TB network to discuss multidrug-resistant TB. This could:

- Identify designated regional expert centres.
- Ensure all healthcare professionals who suspect or treat a case of multidrug-resistant TB are informed about, have access to, and are encouraged to use specialist advisory services for multidrug-resistant TB. This includes the designated expert centre in their regional network and may also include the national advisory service for MDRTB (currently provided by the British Thoracic Society).
- Ensure all cases of multidrug-resistant TB are discussed at the regional multidisciplinary TB team meeting in the local clinical network.
- Formally consider and record the advice from the specialist advisory services for multidrug-resistant TB provided by the designated regional expert centre or the national advisory service for multidrug-resistant TB. **[new 2015]**

10.2.10 Rural Services: Organisational and support factors

10.2.10.1 Evidence to recommendations

Relative value of different outcomes	The primary outcomes include reductions in diagnostic delay, more reactive contact tracing and increases in treatment completion rates
Trade-off between benefits and harms	Benefits of developing networks or links with larger centres to access expertise and other support should assist in ameliorating some of issues faced by the rural sector through improvements to organisation, governance, management and leadership as well as other benefits such as transmission of skills and training and other support mechanisms. All of which should have the knock-on effect to enable the outcomes of interest. Potential risks may be that sub-components of a network may make decisions unilaterally, oblivious to perverse outcomes across the network. This was however, considered low risk and the benefits were considered to out-weigh potential harms. The committee noted the lack of empirical and outcome evidence from evaluations of rural service models for organising, commissioning and delivering TB services. However, they agreed that the expert testimony received showed that a network or hub and spoke model for service organisation and delivery at a supra local or regional level was associated with some indicators of success. In particular key factors they considered were associated with successful TB services for rural communities were shared resources including expertise and resource use (i.e. administration support). However, they noted there was no clear comparative published evidence available to support recommendation development on rural services for delivery of TB, therefore the GDG relied on expert testimony (EP2 & 3) and inference derived from that evidence. The Group noted the benefits of hub and spoke model described in EP2. Although formal long-term outcomes were not available as this system had only been in place since a service review undertaken in 2011 the lead TB nurse clinician did indicate that their day to day experience of the service since implementing the changes had improved treatment completion and contact tracing activities. The Group agreed that successful practice in rural areas (which may have relatively low incidence but large geographical areas to cover) was likely to be due to linkage and affiliation with larger TB centres where resource sharing could improve clinician time with people with TB not only from sharing workforce but also from shared cohort review. The additional benefit of such an approach is that the hub is likely to contain the experts as

	they see many more cases, thus the urban centre act as the reference point for places where fewer cases are seen and thus less expertise is developed. This hub and spoke model was supported by testimony from the North West network (EP3), but again due to the relatively recent implementation of this work although formal evaluations are planned they have yet to generate any measurable outcomes. The committee discussed that in other areas for example cancer networks and paediatrics this kind of model is fairly standard practice with access to expert centres for advice, support and in some cases management with complex cases being an accepted process enabling the services to be more responsive to current events and improved opportunities to share best practice and learning opportunities.
Trade-off between net health benefits and resource use	The committee did not receive any formal economic evidence to support this recommendation as no economic evaluations were identified. However, the committee did consider that collaborative commissioning arrangements were likely to reduce costs and could improve services in rural areas. As could the use of telehealth or other practices through technology enabling the maximisation of contact opportunities between clinicians and people with TB, yet reducing travel across dispersed geographies if this is appropriate for the persons care and the activity or intervention being delivered were recommended.
Quality of evidence	No published evidence was available to support recommendation development, expert papers and inferences of the Committee were used.. Relevant testimony for this section was provided by: ○ EP2: Rurality and service delivery ○ EP3: Practice - North West TB Network: Paediatric TB specialism and a Hub & Spoke delivery model
Other Considerations	<u>Cohort review-support</u> The group recognised that the number of clinical hours nurses spend undertaking cohort review and the potential importance of administrative support in ensuring clinical time is effectively used. However, it was also recognised that cohort review despite introducing a possible administration burden remained a crucial element of TB service delivery to support service evaluation and improvement as well as standard submissions for enhanced surveillance. Therefore the group felt it was important for commissioners to consider administration support for TB nurses via sharing or pooling resources perhaps from a potentially better resourced central base to a more limited rural service for example. <u>Technology</u> The Group noted that in areas where there are geographically dispersed populations such as in rural populations with different levels of incidence, areas should work together and make use of new technologies where possible. The group discussed their experiences of how to overcome some of the issues – and suggested that the cost of sending a nurse specialist or paying for someone to attend outpatients offsets the cost of a smart phone, however as no direct evidence of the impact of this was available they did not feel able to be overly prescriptive in their recommendation on technology.

10.2.11 Recommendations

205. Commissioners in rural areas (working with the TB control board) should consider collaborative approaches to deliver and manage TB services. They could, for example, set up a network including areas with high and low incidence of TB to:

- provide general expertise in the condition and offer expert support and advice on more complex cases
- consider pooling administration support and having arrangements for nursing cross-cover during times of illness or annual leave
- share training opportunities for healthcare professionals and consider protected learning time for continuing professional development activities on TB in those who may encounter TB
- agree a shared cohort review process (see cohort review). **[new 2015]**

206. Commissioners should consider using technology to help patients and staff living and working in rural areas overcome issues such as travel. Technology could also be used to manage staff workload, for example allowing them to attend meetings and consultations virtually. [new 2015]

10.2.12 Local needs assessment

10.2.12.1 Evidence to recommendations

Relative value of different outcomes	The outcome of needs assessment is to enable local areas to consider their population needs and to weigh up the requirements and benefits of different approaches or priorities for action. It looks at what should be done, what can be done and what can be afforded, supporting planning to meet those needs.
Trade-off between benefits and harms	The group agreed that recommendation 2 from PH37 should be incorporated as needs assessment underpins decision making on programmes of work and funding at a local level. No evidence on the benefits and harms of needs assessment were considered by the committee given it is a requirement of health and wellbeing boards under the health and social care act. However, the committee did discuss that on balance there were much greater benefits to taking this approach than not. In particular the data and information generated from needs assessment can be used as a baseline for service evaluation and benchmarking by driving an outcome focused approach. They believed a joint strategic needs assessment (JSNA) can help influence the wider determinants of health such as housing, and may bring economies of scale over individual needs analysis in separate commissioning streams. It can highlight areas of unmet need, and aid decisions regarding allocation of resources. The only potential disadvantage noted by the groups was that in the short term it may require re-organisation and investment to build strategic links with wider partners, and to implement service changes, but that these short terms consequences would be more than off-set by improved outcomes of focussing the commissioning of a service on needs and not historical commissioning decisions.
Trade-off between net health benefits and resource use	There have been no changes to the intent or meaning of the recommendations incorporated from PH37. Whilst they have been re-ordered and adapted to make sense of the decision making process and to fit the current service commissioning and delivery landscape following the Health and Social Care Act the adaptations are not considered to have any new cost impacts as they are incorporated from a published piece of NICE guidance and the requirement to develop needs assessment by health and wellbeing boards is bound in the health and social care act. Given that PHE have committed to providing standardised data-sets on an annual basis to support the implementation of the National strategy, this may actually reduce opportunity costs that may previously have been incurred by local public health teams

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	when collecting and collating data for needs assessment.
Quality of evidence	No high quality analytical studies were identified to support revisions to this recommendation. The evidence on which revisions were made was testimony on a policy and strategy update outlining the 'suite of indicators' PHE would make available annually for health needs assessment and expert consensus by the committee, and the need to consider equity. Relevant testimony for this section was provided by: ○ EP11: Policy update - National TB Strategy
Other considerations	The group discussed the order of the actions in recommendation 2 of PH37 and reprioritised them based a view that decision making should be needs led and it was important for directors of public health (DPH) to think about TB. However they also recognised that not all local authorities would expect to include extensive information on TB in their JSNA if it was not a recognised issue, it was agreed that this judgement should be made by the Director of Public Health in conjunction with local health protection colleagues. Recommendations were expanded where appropriate to recognise the role of health and wellbeing boards in assuring the work of commissioning colleagues and an action was added for them to check that services were being commissioned in response to need. Recommendation on needs assessment content has been reconfigured and updated as Public Health England via their surveillance function will be providing a minimum data set 'suite of indicators' for CCGs and local government to support their TB work. The information relating to this was provided as expert testimony (EP11) and is detailed in the published National TB strategy. A new recommendation was added by consensus, to reflect the need to ensure that health inequalities were considered an important element of the needs assessment and subsequent programme or service development process. It was considered important to ensure that the issues previously highlighted regarding high risk groups in particular those considered under-served were not inadvertently lost in the broader population focus of this guideline. The committee considered it important to note that as TB is a communicable disease there is no justification for not providing a service even if it is not identified as a local priority through the JSNA process. There was also some consideration by the group that in some cases even in an area that may be considered low prevalence there may be high incidence populations.

10.2.131 Recommendations

2 **207. Directors of public health, in discussion with local health protection teams,**
3 **should ensure that TB is part of the joint strategic needs assessment. [2012,**
4 **amended 2015]**

5 **208. Directors of public health should provide commissioners of TB prevention and**
6 **control programmes and TB control boards (see Strategic oversight**
7 **recommendations) with local needs assessment information annually using data**
8 **provided by Public Health England. [2012, amended 2015]**

9 **209. Commissioners of TB prevention and control programmes should ensure**
10 **services reflect the needs of their area, identified by needs assessment. Health**
11 **and wellbeing boards should ensure that local TB services have been**
12 **commissioned based on local needs identified through needs assessment. [2012,**
13 **amended 2015]**

210. Directors of public health and TB control boards should use cohort review (see cohort review) and other methods to collect data on the following, to inform local needs assessment:

- Number of annual notified TB cases (see Public Health England's enhanced TB surveillance data and annual 'suite of indicators'). **[2012 amended 2015]**
- Size, composition (for example, age and ethnicity) and distribution of local at-risk groups[mm]. **[2012]**
- Indices of social deprivation**.[2012]**
- Local statutory and non-statutory services working with these groups. **[2012]**
- Organisation of local TB services, including the composition and capacity of the local multidisciplinary TB team (see the results of local audit) and location of services. This may also include data to support evaluating the need for integrated TB/HIV services including joint clinics. **[2012 amended 2015]**
- Numbers needing enhanced case management (see Adherence recommendations and local cohort review reports).**[2012]**
- Numbers receiving directly observed therapy from the start of, or at any point during, treatment (see Public Health England's enhanced TB surveillance data). **[2012]**
- Evidence of recent transmission (for example, using DNA fingerprinting or surrogate markers such as number of cases in children under 5 years (see 'UK TB strain-typing database' and local incident and outbreak reports). **[2012 amended 2015]**
- Completeness and yield of contact investigations. This includes: proportion of sputum-smear-positive cases with 0, 5 or more contacts identified; proportion of identified contacts clinically assessed; and proportion of contacts with latent TB infection who successfully complete treatment (see also contact investigations).
- Active case-finding initiatives, incident contact investigations and identification of latent TB infection in high risk groups **[2012 amended 2015]**
- Treatment outcomes for everyone grouped according to social risk factors and by the use of directly observed therapy (including rates of loss to follow-up and treatment interruptions – see Public Health England's enhanced TB surveillance data and cohort review, case finding and contact investigation reports). **[2012]**
- Local education and awareness-raising programmes for under-served groups, professionals and practitioners working with them. **[2012]**
- Views and experiences of people with TB, carers and the services working with them. **[2012 amended 2015]**

211. Local needs assessments should also be equity proofed to assess the potential effect of planning, commissioning and policy decisions on health inequalities (see planning and commissioning services in NICE's local government briefing on health inequalities and population health). [new 2015]

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10.2.14 Cohort review

10.2.14.1 Evidence to recommendations

Relative value of different outcomes	Cohort review is defined here as '*A systematic appraisal of the way every case of TB has been managed in a given locality in terms of treatment completion rates and contact investigations over a specified time period*'. The group

[mm] Potential sources include: census data, the National Drug Treatment Monitoring Service, records of locally detained populations, records of homeless people in residential accommodation, the number of rough sleepers and the size of vulnerable migrant communities.

	discussed this definition and the relative importance of cohort review in TB prevention and control. In particular they discussed the need to support treatment completion with appropriate case management practices to minimise poor treatment adherence and the associated risks such as the emergence of acquired drug resistance. They also agreed that issues such as HIV co-infection were important outcomes to discuss as part of cohort review as this may impact on management decisions as described elsewhere in this guideline.
Trade-off between benefits and harms	The group agreed that recommendation 3 from PH37 should be incorporated into the service delivery recommendations. The benefits of cohort review were discussed and it was agreed that in addition to the evidence in the review which identified the benefits of cohort review on contact tracing, they considered it to have additional benefits for service evaluation, and ensuring accountability. Overall they agreed that the process was important in identifying problems and allowing whole system improvement on a continuous basis. The potential disadvantage of cohort review were that it is relatively time consuming and had an administrative burden as discussed elsewhere in this guideline, however, the committee were convinced that from their experience the opportunity cost of undertaking this activity was more than outweighed by the benefit to patient outcomes in their experience.
Trade-off between net health benefits and resource use	The group changed the recommendations to include lead clinician. The group considered whether there were any cost implications for making this change. It was noted that there was no evidence related to cost for this recommendation in the original guidance (which was developed from expert testimony) and as such this amendment could be made, but the recommendation was worded to reflect the flexibility needed for clinicians to decide who may be best placed to attend. The original guidance was for under-served groups therefore the TB case manager was the most important person, as they would be dealing with wide ranging complex needs in addition to the general clinical management of what might be expected in less complex cases – but for the broader population perspective taken here where the case manager may or may not be a clinician but where all cases need to be discussed then the lead clinician is appropriate and should be included in the recommendation for the reasons highlighted above. • There have been no additional changes to the intent or meaning of the recommendations incorporated from PH37. Whilst they may have been re-ordered to make sense of the decision making process and in some cases and adapted to fit to the current service commissioning and delivery landscape following the health and social care act the adaptations are not considered to have any further financial impact.
Quality of evidence	The evidence used to support changes to this section and specified recommendations includes ranged from low to moderate quality. In terms of applicability to the UK context then given the evidence that cohort review is used in the UK it would seem that this particular means of managing the way a service is and can be delivered or improved is transferable to UK service delivery practices. Relevant testimony and evidence for this section was provided by: ○ EP3: Practice - North West TB Network: Paediatric TB specialism and a Hub & Spoke delivery model ○ Service delivery evidence review (Chapter 3: Case Studies appendix G7 and summary statements above) – Summary Statement 9: Cohort Review: New York City and the UK are both reported to use Cohort Review as a way to systematically review the management of every case of TB on the basis of treatment completion, contact investigation and case management process (Bothamley, 2011; Munsiff et al, 2006) as a means for program evaluation, service improvement and ensuring accountability.

	○ Service delivery evidence review (Chapter 4: Effectiveness Review appendix G7 and evidence statements above) - Evidence statement 1: Cohort review can improve contact tracing in TB patients. Both effectiveness studies were judged to be of moderate (+) quality via the critical appraisal process. • The evidence reviewed did not impact directly on the changes to the recommendations made by the committee these changes were reached on the basis of expert consensus of the committee.
Other considerations	The committee discussed the scrutiny role of local government and considered whether they had a specific role in the cohort review process. However, on reflection it was agreed that scrutiny functions in a lot of different ways in local authority so the committee thought there would be a risk of trying to define a role for it here and that it was better to leave local authorities to decide how and if to use it. Frequency and location of cohort review The group noted that a quarterly cohort review meeting should be the minimum but the existing recommendation implied that this is how often they should meet; this recommendation was updated to reflect this, but not to preclude more regular meetings. Some members of the committee participated in /encouraged cohort review meetings more often to fit in with related planning and evaluation activity. However, it was recognised that cohort review meetings could be time consuming. Therefore, the group agreed to add that 'cohort review meetings should, where possible, be combined with others'. The rationale for this was based on the expert testimony (EP2) about some of the issues that occur in rural services when covering large geographic areas and managing administration and meeting needs particularly cohort review which was considered crucial but resource intensive. In addition the committee discussed their experiences in a variety of settings and the need for ensuring efficiency in using practitioners' time so if meetings could be combined to reduce opportunity costs this would be beneficial. It was suggested combining meetings and using technology to overcome geographical/logistical barriers may help. Additionally by reducing the need for a series of different but crucially inter-related meetings, especially as some team members may need to be at multiple meetings for different reasons, ensuring time could be used as efficiently as possible or that geographical issues did not impact on attendance. Administration support It was agreed that administration support in particular to support cohort review but also for other service monitoring and evaluation was important. The developed recommendations around this issue. They reflected on the fact it was considered a particularly resource intensive element of a nurses. The committee were aware of a rural service that was over-stretched by a lack of administration support resulting in the potential breakdown of the cohort review process but also service provision due to unmanageable resource pressures on delivering treatment and maintaining appropriate records for cohort review and other system needs. The testimony from a rural service highlighted its benefits. Key information for cohort review The recommendation on standardised information was updated to ensure HIV results amongst other things were considered explicitly. The group agreed that this detail was important to highlight the breadth of the information that should be expected at cohort review, to ensure relevant information for service evaluation and improving outcomes were provided as examples given the purpose of the cohort review process. Attendance/leadership at cohort review meetings The recommendations on attendance were updated as the group considered it important that the lead clinician was in attendance where possible in addition to the case manager. The group wanted to strengthen the recommendation from

could to should as they believed there would be benefits if issues about managing clinical complexity are discussed. However they did not have evidence to make to change. Another benefit of the lead clinician attending would be in relatively low incidence areas where expertise may be less developed and the lead clinician may gain the most from involvement in the cohort review process and the cycle of evaluation and service improvement it supports. However, overall the committee were unable to strengthen this recommendation.

- The GDG discussed that in order for this to happen then cohort review should be a 'programmed activity' in their work scheduling and this was added to the recommendation, the risk of not adding this was that clinicians would not be enabled to attend cohort review (a key audit and evaluation activity to improve outcomes) and that this could impact on contact tracing potentially increasing transmissions and reductions in treatment completion potentially increasing likelihood of MDRTB or other complications.

The group agreed to broaden the people who could chair as improving flexibility would increase likelihood of identifying someone suitable.

Where relevant recommendations were updated to reflect the need to include health and wellbeing boards and TB control boards as an appropriate group to receive feedback from cohort review. Not reflecting their roles may hamper implementation and an understanding of their positioning within the system.

Examples were added to recommendations where relevant to support implementation. The group thought this was important to ensure evaluation was completed effectively, as based on the committee's experience important issues of relevance to cohort review were not always considered.

10.2.15 Recommendations

212. TB control boards and prevention and control programme leads should initiate, audit and evaluate cohort reviews in their commissioning area. Quarterly cohort review meetings should take place in the area covered by the programme. Combine these meetings with others if possible, or make use of technology to make it easier for clinicians and case managers to attend. [2012, amended 2015]

213. TB case managers should present standardised information on each case, including: demographic information, HIV test results, pre-treatment and ongoing status (clinical, laboratory, radiology), adherence to treatment and the results of contact investigations. [2012, amended 2015]

214. TB case managers and key allied professionals from the TB prevention and control programme should attend cohort review meetings. This could include the lead clinician (who may or may not be the case manager). Either a paediatrician with training and expertise in TB management or a paediatric infectious disease specialist should be present when cases of children with TB are presented. [2012, amended 2015]

215. The chair of the cohort review should not work for any of the TB services included in the review. Examples of possible chairs include a public health consultant, a specialist physician or a senior TB nurse, preferably from a different geographical area. Alternatively the chair could be a representative from the local Public Health England health protection team or the TB control board. [2012, amended 2015]

216. Multidisciplinary TB teams, in conjunction with Public Health England units and the TB control boards, should collate and present cohort review data on TB treatment and the outcome of contact investigations at the review meetings. In addition, progress towards national, regional and local service targets should be presented. [2012, amended 2015]

217. TB control boards directors of public health and local public health consultants should ensure outputs from the cohort review feed into the needs assessment for TB services. TB control board directors should attend the cohort review at least once a year. [2012, amended 2015]

218. TB case managers should feed back promptly to multidisciplinary TB teams on issues identified as a result of cohort review. The results of the cohort review should be collated locally and agreed by the chair before being fed back to TB control boards, commissioners and health and wellbeing boards regularly and via needs assessment. [2012, amended 2015]

219. People participating in a cohort review should review the results and evaluate local services (for example, auditing adverse outcomes, rates of culture confirmation, treatment completion rates or time to diagnosis). [2012, amended 2015]

10.2.16 Commissioning multidisciplinary TB support

10.2.16.1 Evidence to recommendations

Relative value of different outcomes	N/A
Trade-off between benefits and harms	In agreement with previous NICE guidance on service configuration the committee agreed that multidisciplinary teams make better decisions than individuals. The committee did not consider there were any dis-benefits to recommending the commissioning of multi-disciplinary teams to support delivery of TB services.
Trade-off between net health benefits and resource use	There have been no changes to the intent or meaning of recommendations incorporated from PH37. Whilst they have been extrapolated to from under-served groups to the whole population in some cases and adapted to fit to the current service commissioning and delivery landscape (as noted in the committee discussions for oversight and commissioning) following the health and social care act the adaptations are not considered to have any financial impact as activities already recommended by NICE in PH37 have not changed measurably. The group did not hear any formal economic analysis to support administrative support. Whilst administration support has been recommended it was decided that this would not necessarily require new resources but could in some circumstances mean that the administration support available locally could be drawn upon to support TB work. If the TB incidence locally was considered high such that new administration resources may be required as the committee felt that administrative support was vital to the TB service, they considered that the cost of employing an administrator would be off-set by the nurse time it could free up, which in turn was likely to improve outcomes, and potentially lead to future savings. This is supported by the committees understanding of the expert testimony on the effect of a TB nurse having gained administration support from collaborating with a larger centre and the expressed benefits to clinical practice and capacity to deliver clinical activities, in particular DOT. This

	convinced the committee administration support would be beneficial particularly due to the likely health benefit on treatment completion rates, and reductions in loss to follow-up compared with potential resource use. Originally the recommendations in PH37 had not explicitly stated the 1:20 and 1:40 ratio was for active TB (in the recommendation as it had been covered by some prefacing text prior to the recommendations in the original guideline which will not be carried over). The committee considered this may be a risk when considering the trade-off between net health benefits and resource use. They therefore, clarified this by adding a recommendation for latent TB based on consensus and the experience of the committee specifically TB nurses of the different time allocation needed for latent TB. The group believed without this commissioner may interpret the case ratios relevant to all TB cases i.e. both active and latent which is incorrect. The inclusion of cohort review and MDTB team meetings as programmed activity was discussed as this may be considered a cost implication by commissioners. However, as the purpose of these meetings was to discuss and overcome case management issues such as loss to follow-up or improvements in treatment completion and reducing delays in diagnosis the committee agreed the potential opportunity cost would be more than off-set by the improvements in outcomes the meetings would generate from their expert opinion. The GDG agreed with the discussions and conclusions.
Quality of evidence	The committee recognise that the evidence on which changes to these recommendations from those published in PH37 were primarily based on expert testimony and descriptive evidence in the case study review (except some limited evidence on staff:case ratios highlighted below). Whilst they agreed this may limit the quality of the evidence and include a certain amount of uncertainty as it was not experimental in nature and therefore had not controlled for bias they were convinced the clarifications and additions made would in their expert opinion result in more health benefit than resource use as described. Relevant testimony and evidence for this section was provided by: ○ EP2: Rurality and service delivery ○ EP3: Practice - North West TB Network: Paediatric TB specialism and a Hub & Spoke delivery model ○ EP8: Practice - Experience of people who use TB services ○ Evidence Review – Chapter 3 case studies: Summary Statement 7 appendix G7 and summary statements above: Staffing. Staffing ratios of nurses (or other staff) differ across the case study areas from 1:12 in NYC; 1:18 in the Netherlands and 1:35-45 in Barcelona. There is no UK data available to provide a national picture of TB staff:case ratio (Boer and de Vries, 2011; Bothamley, 2011; Cayla and Orcau, 2011). ○ Evidence review - Chapter 4 effectiveness review: Bothamley 2011 (-) surveyed big cities across the UK on various TB targets including whether they had achieved the target of 1:40 nurse to TB case ratio. The survey identified that cities which had not achieved this ratio were more likely to have more than 6% loss to follow-up ($p<0.05$), and less likely to use World TB day as a means of promoting TB awareness and outreach. Of note this is one of the twelve studies that utilised an audit design, national/regional/local reports or evaluation, or a cross-sectional design were classified as low quality evidence (–) due to the high potential for confounding and bias that can occur in these types of study designs. See appendix G7 for further detail of this study. • Given the limitations of the evidence available, the recommendations were reached on the basis of expert consensus of the committee.
Other considerations	○ Bullet 1: In relation to a case manager in the MDTB team, the group reflected on the case manager: number of cases ratio (1:40) recommended in PH37, as well as the wording in the British Thoracic Society guidance/guideline in relation to nurse/staff: case ratio. They felt that this

recommendation should note a ‘minimum’ of 1 wte case manager, as the group reflected on the evidence they had received on staffing ratios from other countries for example, in New York, there is a ratio of 1:12 staff to people with TB further supported by other evidence from the review that suggests those places where this ratio is met in the UK have improved outcomes– Bothamley et al 2011 and Cayla & Orcau 2011 (Summary statement 7: staffing). They considered that staff:case ratios was a core under-pinning factor in the effectiveness of TB service delivery outcomes despite the lack of high quality comparative evidence available to support their expert consensus.

- The group acknowledged that latent TB (LTBI) was not originally captured in the recommendation and were aware they have not seen any evidence about staffing ratios in relation to LTBI. In practice they discussed that there is a pragmatic assumption that LTBI is equal to 0.5 active cases therefore a ratio of 40 cases of LTBI per 1 WTE case manager for standard case management and 80 cases of LTBI per 1 WTE case manager for enhanced case management is assumed. The committee discussed that it was important for this detail to be included in the service delivery guidance to support commissioners in considering local population needs when commissioning services with sufficient manpower to deliver services as LTBI treatment was not resource free and delivery was not absorbable into current services. It may also need to be considered differently than services for active TB in terms of organisation of the service dependent on local population needs and this may have significant variation across the country dependent on population epidemiology. Therefore an additional bullet was added to reflect the need for differentiating between the case:staff ratio needed for LTBI.
- In relation to multidisciplinary TB teams, the group considered the evidence from expert testimony which had highlighted the important role administrative support can offer in provision of TB services. The group were also aware from personal experiences; supported by comments from EP2 around access to suitable IT infrastructure for TB nurses and considered this a risk to both efficient and safe patient record and data management practices as well as affecting capacity to effectively and safely share data if required. Therefore, the group agreed by consensus that ‘administrative support’ and ‘access to IT’ should be added to the recommendation.
- Bullet covering “range of clinical”, added ‘and laboratory’ as the group considered it was important to clarify the need for both clinical and laboratory specialities, as the term clinical does not capture this important field for TB.
- In relation to the ‘Have access to funds’ bullet point- The group noted at present it is unclear how this is done systematically across TB services in the UK particularly around support for accommodation local government and NHS were added to clarify who the committee considered responsible. Further use of the term incentives was discussed and altered the to ‘support/enablers’ the reason being ethical issues around incentives and widening inequalities in other areas of treatment, from a CCG perspective may mean not funding incentives but as the recommendation means funding to enable treatment completion or other service elements it is not an incentive but a support mechanism for people with TB.
- In relation to the awareness raising bullet, the group noted this should be cross referenced with the relevant recommendations in the clinical guideline which gives more details including the content and format of information. Local government and CCGs were added as the acting bodies for the same reason as above.

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10.2.171 Recommendations

220. Commissioners should ensure multidisciplinary TB teams:

- Have the skills and resources to manage the care of people with active TB who are not from under-served groups. (A minimum of 1 whole-time equivalent case manager is recommended per 40 incident cases needing standard management.) **[2012, amended 2015]**
- Include at least 1 TB case manager with responsibility for planning and coordinating the care of under-served people and those with active TB who receive enhanced case management. (One whole-time equivalent case manager is recommended per 20 incident cases needing enhanced case management.) **[2012, amended 2015]**
- Have the resources to manage latent TB care in under-served groups and the wider population. (One whole-time equivalent case manager is recommended per 40 latent TB cases needing enhanced case management and per 80 latent TB cases for standard case management). **[new 2015]** Update 2015
- Include a range of clinical specialties in the multidisciplinary TB team, including paediatrics, infection control and respiratory medicine. **[2012]**
- Have regular attendance at these multidisciplinary team meetings and cohort review meetings for all team members included as a programmed activity as part of their work planning. **[new 2015]** Update 2015
- Have the skills and resources necessary to manage the care of people with complex social and clinical needs (either directly or via an established route). This includes the ability to provide prompt access (or if necessary, referral) to skilled outreach and advocacy workers who can draw on the services of allied practitioners. The aim is to address people's housing, asylum, immigration, welfare, substance dependency and other health and social care needs. (The allied practitioner support should include both a specified housing officer and a social worker.) **[2012]**
- Can provide rapid access TB clinics for all cases, including under-served groups. **[2012]**
- Provide administration support to TB nurses and case managers so they have capacity for clinical and case management work in line with the standard case management or enhanced case management ratios. This should include giving TB nurses access to computer hardware and software. **[new 2015]** Update 2015
- Have the resources to provide a continuous service throughout the year, ensuring the TB service accounts for the following to manage continuity of care:
    - planned absence (for example professional development, mandatory training, annual, maternity or paternity leave)
    - unplanned absence (such as sickness absence). **[2012, amended 2015]**
- Can provide prompt access to a professional who has training and experience in assessing and protecting children and vulnerable adults at risk of abuse or neglect. **[2012]**
- Have access to funds through local government and clinical commissioning groups that can be used flexibly to improve adherence to treatment among under-served groups. For example, funds could be used to provide transport to clinics, to provide support or enablers for treatment, or for paying outreach workers or community services to support directly observed therapy. Funds may also be used to provide accommodation during treatment (see rapid access TB services recommendations). **[2012, amended 2015]**
- Have the resources to provide ongoing TB awareness-raising activities for professional, community and voluntary (including advocacy) groups that work with populations at high risk of TB (see recommendations on raising and sustaining

awareness of TB and Providing information for the public about TB). These resources could be financed by local government or clinical commissioning groups. **[2012, amended 2015]**

10.2.185 Non-clinical roles including TB support workers

10.2.18.16 Evidence to recommendations

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Relative value of different outcomes	The group agreed that reducing delays in diagnosis, improving contact tracing outcomes and supporting treatment completion were the highest priority outcomes for recommending consideration of employing TB support workers.
Trade-off between benefits and harms	These recommendations were developed based on both expert testimony from a variety of experts and the service delivery review case studies and effectiveness chapter. The benefits considered by the committee included the capacity for support workers to engage more effectively with people at risk of or diagnosed with TB specifically that non-clinical support workers could have manifold benefits on reducing delay in diagnosis, improving contact tracing and supporting treatment completion either as a result of direct intervention by delivery of actions by appropriately trained support workers or by freeing up TB nurse time to enable improved outcomes in these areas. Harms considered by the committee were primarily around the concern that commissioners may consider that support workers could be employed in place of clinical staff such as TB nurses, which is not the intention of the recommendations. The group wanted to make it clear that any additional resource should be considered as extra and should not replace clinical staff or the need for clinical leadership.
Trade-off between net health benefits and resource use	The group recognised there may be cost implications for these recommendations and received economic evidence on the cost impact of support workers. The group heard evidence that in terms of resources, support workers are employed at a AfC band 3 to 6 depending on the tasks they are employed to undertake and the training involved. They heard evidence that in some areas where support workers free up the time of a TB nurse then this could be cost saving. However, in circumstances where the support worker does not free up nurses time then the additional cost of employing a support worker will be incurred. In terms of outcomes, the evidence presented was qualitative in nature but the committee believed that support workers played a vital role in supporting nurses and were often viewed as more approachable by people with TB. They believed that even with uncertainties in all likelihood this was in fact going to have a lower cost impact than presented as the benefit included in the threshold analysis were only one facet of benefits in terms of treatment or other outcomes such as the patient experience and unquantifiable benefits in non TB related outcomes such as self-esteem and confidence such that the value included in the threshold analysis was likely to underestimate the paybacks likely to accrue. Therefore, the committee felt that on economic grounds support workers should be recommended as there only needs to be a small benefit to justify the costs, especially in circumstances where support workers could be used to free up nurse time. The costings work highlighted the diversity and range of agenda for change bandings staff were employed within the UK ranging from afc band 3 to band 6.

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	The committee were surprised by the higher bandings, but agreed that the rate should be commensurate with the tasks assigned to a support worker and if case management and cohort review activities were deemed appropriate the member of staff appropriately trained then this would seem suitable. But it was clear that support workers should not take the place of clinical staff and should be supported by appropriate supervision and adhere to governance arrangements when undertaking their agreed activities. .
Quality of evidence	The group noted that the evidence on which they had based these recommendations were a mixture of expert testimony which they considered low quality as described elsewhere as well as the case studies again considered of low quality due to their discursive nature and low to moderate quality comparative studies. Overall the evidence was mixed but considered relatively comprehensive compared to other areas on which they had agreed to make recommendations. However, as with other areas of the service delivery recommendations much of the evidence based was their own personal experiences of how services are delivered in the UK with the support of non-clinical staff and recognise that this remains a consensus driven recommendation from their expert opinions. Relevant testimony for this section was provided by: ○ EP2: Rurality and service delivery ○ EP4: Practice - the Leicester experience including rapid radiology referral model ○ EP7: Contact Tracing – incident investigation process in congregate settings ○ EP8: Practice – Experience of people who use TB services ○ Cost impact analysis – Chapter 5 – TB support workers (see appendix G7 for further details) ○ Evidence Review – Case Study chapter – summary statement 4 appendix G7 and summary statements above: contact tracing and 7 staffing highlighted that different staff were involved in a variety of different aspects of service delivery in different countries. Applicability may be moderated by having different healthcare systems although there is no reason to suspect that as long people were trained appropriately that non-clinical staff could not deliver appropriate elements of TB services in the UK. For example all areas included in this case study chapter of the review deliver contact tracing using the same method (stone in the pond/concentric circle), with variation found in the staff who delivered it. In Barcelona community health workers recruited as 'peers' of the target group are involved in delivery of contact tracing. In the Netherlands, medical assistants support delivery of contact tracing and in NYC Public Health assistants deliver contact tracing: This may contribute positively to the effectiveness of the contact tracing activity – see Effectiveness review. In the Netherlands medical assistants also support public health nurses to deliver case management including DOT in clients with complex needs in community based clinics. In NYC trained Public Health Assistants are responsible for most case management including DOT, active case finding in addition to contact tracing activities as well as providing formal case review as part of the cohort review process. These support workers are likely to off-set the workload of specialist TB nurses (Cayla and Orcau, 2011; Ospina, 2012; Boar and de Vries, 2012). In the UK most of the tasks described are undertaken by specialist TB nurses. ○ Evidence review – Chapter 4 - Evidence statement 5 appendix G7 and evidence statements above: Community health workers can increase contact tracing in immigrant communities. The evidence is partially applicable to TB service delivery in the UK as the demographics of TB patients and contact tracing policies in the UK may vary from that in Barcelona, although the technique used i.e. stone in the pond does not. The results of the study may be most applicable to areas of the UK where there is a high incidence of TB in people from immigrant communities.

	○ Evidence Review – Chapter 4 - Evidence statement 7 appendix G7 and evidence statements above: Peer educators can increase TB screening in hard to reach groups, Hall et al, 2010 (–). This evidence is directly applicable to TB service delivery in the UK as it is a UK based study. However, the results may be most applicable to areas of the UK where there is a high incidence of TB in hard to reach people.
Other considerations	Non clinical workers are currently employed in a variety of roles within TB services in the UK which is evidenced either from the testimony received (EP 2, 4, 7, 8) as well as from the personal experience of members of the committee for example DOT workers and peer support workers in London; and healthcare support workers in Manchester. The committee discussed their experiences and the evidence. In the case studies it is clear non clinical support for TB is widespread. There are a variety of roles people are trained to deliver across the spectrum of TB control and care ranging from enhanced case management and cohort review tasks, active case finding and contact tracing (service delivery review summary statements 4 & 7; Evidence statements 5 & 7). The committee discussed the diversity of the workers available across the case studies as well as those found in the UK and agreed that the recommendations must remain flexible to local variation based on local needs, and should be a clinician-led service with appropriately trained and supervised support staff. The group recognised the importance of having peer support in services either from a voluntary or formal perspective, which is covered briefly elsewhere (see Raising and sustaining Awareness of TB recommendations above) but felt that a specific recommendation outlining the breadth of activities and considerations regarding governance was warranted The committee considered that making services as accessible as possible involves taking a range of factors into account. These include: people's language, literacy level, age, ethnicity and gender, as well as any disability, mental health or substance dependency-related problems. Location of clinics, transport to and from them, opening times and the provision of appropriate communication materials and prompts are all equally important. However, the evidence available had not enabled them to make broader recommendations than to consider employing non-clinicians to support service delivery. The committee therefore discussed how to frame the recommendation regarding ensuring that workers had the skills to engage with their local community for awareness raising activities and the cases likely to manifest. It was suggested that similar to Barcelona, where specific cultural issues were a potential barrier perhaps recruiting workers from specific communities would be beneficial, EP8 was also discussed where testimony identified that a former street drinker when working as a peer educator visited a wet house and had initially been unable to convince a number of people to visit the mobile X-ray unit until they had disclosed their own background. However, despite this being an example of support workers from affected community groups the committee were also directly aware of examples where support workers did not need to be from a specific background to empathise with people and be effective in encouraging them to attend for testing or accept treatment. The therefore group agreed that to support TB services workers needed to have the skills and abilities to work with the variety of people their service may be targeting and did not absolutely need to be from specific cultural, racial or behavioural backgrounds as long as they had the skills to engage with different groups effectively. The committee discussed and agreed that governance issues and the need for service level agreements along with accountability was included to enable support workers to be employed as they are not bound by the same professional codes as nurses and doctors. A recommendation on hits was added.

10.2.19 Recommendations

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221. TB control boards and local TB services should consider employing trained, non-clinically qualified professionals to work alongside clinical teams to agreed protocols, and to contribute to a variety of activities. Examples of this may include awareness raising and supporting patients to attend appointments (including other health and social care appointments). They could also help with collecting samples, contact tracing, case management including directly observed therapy and cohort review, or any other aspect of the service if:

- they are trained to deliver the intervention or processes effectively
- they are supported, mentored and supervised by a named case manager such as a TB nurse
- they have the skills to monitor, evaluate and report on their work practices and outcomes to maintain a process of ongoing evaluation and service improvement in relation to cohort review (see cohort review recommendations). **[new 2015]**

222. TB control boards should ensure that people working in the TB service have the right knowledge, engagement, advocacy and communication skills to meet the needs (for example language, cultural or other requirements) of all the groups they may work with (see needs assessment). [new 2015]

223. Commissioners should consider different needs across traditional geographical and organisational boundaries are taken into account. Put agreements in place so that staff can work across these boundaries, covering the whole service or TB control board area if appropriate. [new 2015]

Update 2015

224. Commissioners and TB control boards should ensure they put in place appropriate governance (including clear lines of accountability and extension of scope of practice) and data sharing practices and agreements. This includes ensuring they are part of service level agreements between NHS and non-NHS services, for example the third sector or local government, and appropriate training has been completed. [new 2015]

10.2.20 Contact investigations (active case finding in underseved groups & incident and outbreak response)

10.2.20.1 Evidence to recommendations

Relative value of different outcomes	The group considered that reducing delays in diagnosis, identification of secondary cases and more rapid initiation of treatment were the most important outcomes resulting from these recommendations. These were considered the highest priority outcomes as they would lead to other beneficial outcomes including reduction in risk of transmissions, improved availability primary prevention of TB and reduction in both morbidity and mortality associated with TB.
Trade-off between benefits and harms	The benefits of the new recommendations were that more systematically planned contact investigations should result in earlier diagnosis of cases, rapid access to chemoprophylaxis where required and a reduction in the likelihood of transmissions, particularly in congregate settings and high-risk populations. This was supported by evidence showing that the use of mobile screening

	increased case finding rate in under-served populations (ES6), rapid access referral triggered by radiology (ES8), and increasing epidemiology links based on exposure (ES3) The committee did not consider these improved organisational processes to result in any harms other than potential unwarranted anxiety in the people subsequently found not to have been a case and the harms from treatment described elsewhere in this guideline, particularly if treatment was initiated as a result of a false positive diagnosis, although the risk of that was considered no greater in the scenario's discussed than during any other diagnostic investigations recommended within this guideline. When discussing incident and outbreak control, the group consider the benefits to be apparent to all in TB services but considered that the current adhoc arrangements would be best replaced with document roles and responsibilities allocated to personnel within existing TB services. The harms of not doing this mean that the service is not in a position to respond as quickly and efficiently and with thus put more people at risk if infection.
Trade-off between net health benefits and resource use	The group heard evidence (Service delivery effectiveness review in appendix G7 - ES6) that mobile digital radiography for active case finding can be a cost-effective use of resources (ICER £10,000/QALY) in under-served groups in the UK, compared with passive case finding. The committee considered that this evidence was strong enough to warrant explicitly recommending digital mobile radiography. The group heard no cost benefit evidence on incident or outbreak response activities as these activities were a requirement and a core role and responsibility of the health protection workforce with the expectation that this workforce can be mobilised to support these activities and thus had no cost implications.
Quality of evidence	Relevant testimony for this section was provided by: ○ EP7: Contact Tracing – incident investigation process in congregate settings ○ Evidence review – Chapter 3 Case Studies appendix G7 - Summary Statement 5: Targeting high risk groups. All case study places actively target high risk groups, although the approaches used differ. Pre-entry screening is well established in NYC and Canada and has been very recently introduced to the UK. NYC, Rotterdam and London also make use of outreach and mobile x-ray units to diagnose hard to reach groups such as the homeless (de Vries et al, 2007 and 2014; Hayward et al, 2010). In the UK this aspect of the service is only widely used in London (de Vries et al, 2007 and 2014; Hayward et al, 2010). ○ Evidence review – Chapter 4 effectiveness review appendix G7 - Evidence statement 6: Mobile screening can improve treatment completion and active case finding in hard to reach people. There is strong evidence from two studies (London UK (++),1 Netherlands (+)2) that a community based mobile radiography unit can increase active case finding by between 23-30% in hard to reach groups in an urban setting, compared with passive case finding/before mobile screening was introduced. The evidence is directly applicable to TB service delivery in the UK. This is because there are no obvious differences in the delivery of mobile screening in the included studies compared to how it could be delivered in the UK ○ Cost impact analysis - Chapter 5:TB support workers see appendix G7 for further details The addition of recommendations was therefore agreed by the committee based on their expert consensus despite the potential limitations of the evidence available.

Other considerations	The group agreed that the recommendation on contact investigations in PH37 should be incorporated into the service delivery guidance, however this and new elements of the recommendation have been integrated into the updated section of the NICE version of the guideline on 'Case Finding' under a variety of headings including 'Active case finding in under-served groups', Incident and outbreak response, but for the purpose of presenting the development of the recommendations and discussions by the committee and GDG it is presented under the single heading of contact investigations here. It was agreed to maintain the examples that are relevant to under-served groups to ensure these scenarios are considered explicitly due to the transmission risk in these settings in addition to the usual identification of close contacts in the clinical guideline. However to account for additional scenarios based on new recommendations included in this section other examples were added as transmission sites in the relevant recommendations. These examples are of high risk congregate settings and are included in the recommendations. • These examples are based on expert testimony (EP7) and the experience of the GDG in running or being involved in these investigations, they are not intended to be exhaustive. It was also extrapolated to say 'people' with complex social networks, although it is likely to remain focused on under-served groups there may be others who have complex social networks. They agreed that there is no clinical or public health reason for this to remain focussed on under-served groups only. The group felt it should be clarified that MDTB teams and local public health/health protection team should take the lead for active case-finding, but that MDTB teams should refer potential incidents to the local health protection team for additional support when a risk assessment for a large scale investigation may be required, to enable mobilisation of the wider health protection workforce may be needed. The group agreed that the settings could be identified by 'looking at social networks' (replacing 'social network analysis'). The reason for this is that this is a pseudo-scientific term that may appear to require more specialist expertise to deliver than is the case. This could have the unintended consequence of appropriate investigation routes being overlooked. The group noted that these recommendations are relevant to all children not just 'hard-to-reach' and should be extrapolated. The reason for the specificity previously was as a result of the focus of the previous guideline, they agreed there is no clinical or public health reason for this not to be all children, and could if not extrapolated, result in contact tracing activities that pose a risk for the population as potential transmissions will not be effectively controlled, further, children may be at risk of undiagnosed TB. New recommendations have been added based on (EP7), to account for contact investigation in those groups not classified as under-served but where there are cases with transmission risk such as in congregate settings like schools and workplaces. The groups agreed the recommendations based on consensus and their experiences of conducting such investigations in a variety of these settings. This took into account the need to take a standardised and structured approach based on agreed risk assessments and decision making steps for determining the breadth of the investigation, as described in all of the active case finding recommendations in this guideline. Whilst one recommendation suggests setting up incident response teams, this is not intended to imply this is a new workforce but that there may need to be identification of a group of personnel in a TB control board area (for example) who will come together to manage these scenario's. It is the experience of the committee this already happens on a more adhoc basis. The group therefore agreed that it would be best practice to have these roles/responsibilities identified more systematically to improve reactivity to such events and to ensure that it was clear to whom these incidents need reporting again this would have no cost implications and did not need to be considered explicitly from a cost effectiveness perspective.

The recommendations on incident and outbreak response are therefore more to do with organisation and planning of these resources more effectively to reduce variation. The committee noted that from their experience resources within the system would be diverted to undertake such investigations. Whilst this may be an opportunity cost for other areas of public health work this was more than off-set by the reduction in future morbidity or potential mortality from identifying and treating all cases of disease, therefore the committee considered that the benefits would outweigh any costs.

10.2.212 Recommendations

225. TB control boards should ensure there is enough capacity available to them to manage a sudden increase in demand such as:

- TB contact investigations (for example incidents in congregate settings)
- large scale active case finding initiatives in under-served groups in the community
- outbreaks in a variety of settings or sites where transmission risk may be high, including but not limited to schools, workplaces, hostels and prisons. **[new 2015]**

Active case finding in underseved groups

226. Multidisciplinary TB teams should follow NICE recommendations on contact tracing (see Case finding section).They should coordinate contact investigations at places where the person with TB spends significant amounts of time. Examples could include pubs, crack houses, parks and community centres. The aim is to help identify people who have been living with them and people they frequently socialise. [2012]

227. Multidisciplinary TB teams dealing with someone from an under-served group should work alongside health and social care professionals known to them to help trace relevant contacts. They should also work in partnership with voluntary, community and statutory organisations to conduct outreach contact investigations. [2012]

228. Multidisciplinary TB teams should, if available and appropriate, encourage peer educators or TB programme support workers (see Non-clinical roles including TB support workers) to help with contact investigations involving under-served people who have complex social networks. [2012]

229. Multidisciplinary TB teams in discussion with local Public Health England health protection teams should consider using digital mobile X-ray for active case-finding in settings identified by looking at social networks as places where under-served people at risk congregate. They should also provide the necessary support so that multidisciplinary TB teams can use strain-typing and social network analysis to ascertain where transmission is occurring in the community. (Examples of transmission sites may include pubs, crack houses, hostels and day centres.) They should focus on active case-finding in the settings identified. [2012, amended 2015]

Incident and outbreak response

230. Multidisciplinary TB teams should coordinate incident or outbreak contact investigations at places where the person with TB spends significant amounts of time. Examples include workplaces, schools, colleges, universities, childcare settings. The aim is to help identify people they frequently spend substantial time with as outlined in the Active case finding section. [new 2015]

231. Multidisciplinary TB teams should refer any incident in a congregate setting to the local health protection team for risk assessment within 5 working days of suspicion of a potential incident. They should tell the local TB control board a referral has been made. [new 2015]

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232. TB control boards working with local health protection teams should set up or have access to an incident team that will:

- undertake an incident risk assessment and provide advice
- support or undertake contact investigations
- provide information and communication support to the multidisciplinary TB team, the local director of public health, the setting where the incident has occurred and the people affected including:
    - written advice printed or by email
    - question and answer sessions
    - telephone advice
    - media engagement.
- Gather and collate data, and report on outcomes to measure the effectiveness of the investigation (for example, offering testing to all people identified at risk and monitoring uptake).
- Report back to TB control boards at appropriate times. This includes when outcomes of initial investigation of people classified as close contacts are available. It also includes when a decision is made to broaden the investigation to the next stage using the concentric circle method for risk assessment). **[new 2015]**

Update 2015

233. When incidents have been identified, multidisciplinary TB teams in discussion with local Public Health England health protection teams could also provide support for strain-typing and other analysis to ascertain where transmission is occurring. (Examples of transmission sites may include workplaces, schools, colleges, universities, childcare settings). [new 2015]

234. In all types of contact investigation scenario (active case finding, incident or outbreak investigations) multidisciplinary TB teams should investigate all people who have been in contact with children who have pulmonary or non-pulmonary TB to identify the primary source of infection. If necessary, they should look beyond immediate close contacts to find the source. [2012, amended 2015]

10.2.22 Rapid-access TB services

10.2.22.1 Evidence to recommendations

Relative value of different outcomes	The group agreed that the priority outcome for rapid access TB services was reducing delays in diagnosis. They agreed this may have secondary outcomes of reducing diagnostic delay would include reduction in risk and rates of transmission of TB, reductions in loss to follow up particularly in under-served groups and an overall reduction in the morbidity and mortality

	associated with delays in treatment initiation.
Trade-off between benefits and harms	The group agreed that recommendations on 'rapid-access TB services' from PH37 should be incorporated into the service delivery guidance. The benefits of these recommendations and the adaptations agreed by the committee include reduction in time to diagnosis, reduction in possible complications as a result of delay as well as reduced risk of onward transmission. They agreed this may have particular benefit to under-served groups by reducing likelihood of loss to follow-up if they are required to turn up for an appointment. The considered improving the speed of accessibility for under-served groups may have a noteworthy impact on treatment completion, contact tracing and reducing delays in diagnosis. If someone from these groups has to wait for the next clinic space they are unlikely to turn up. It was therefore felt important to ensure TB services can respond flexibly and proactively to referrals by, or on behalf of, under-served groups, rather than following the standard referral process. It was also recognised that having rapid access referrals would also have the knock-on effect of improving access to everyone with TB. Self-referral recommendations were revised to include "by people who suspect they have TB" rather than just under-served groups. This extrapolation was agreed as identifying people early and preventing transmission was a core rationale for this whole section and enabling people to self-refer may be a core offer to support this (particularly if awareness of signs and symptoms is raised which may in turn reduce transmission risks). Harms the committee did discuss were the impact self-referral might have on numbers and workload and potential risk to service capacity . However, the evidence received from expert testimony (EP12) and provided by committee members from their expert experiences indicated this was not realised in practice. The group agreed by consensus that the benefit of having walk in access is highly likely to outweigh any potential harm in terms of increasing workload due to the reduction in risk of onward transmission and reduction in time to diagnosis with associated potential complications as a result of delay.
Trade-off between net health benefits and resource use	This recommendation was incorporated from PH37 the amendments in the recommendation have not changed intent or meaning, they have only clarified under what circumstances different referral timelines should be considered. The addition of 'direct referral from emergency departments' has been considered more extensively elsewhere in this chapter from the perspective of net-health benefits and resource use.
Quality of evidence	The changes to this set of recommendations have been primarily for clarification purposes. Additions have not been based high quality comparative evidence but on a combination of expert testimony and consensus discussions by the committee. Whilst the expert testimony is considered applicable is not without inherent bias as it is based on opinion and not high quality experimental or observational studies. It is therefore considered by the committee to be of low quality from the perspective of the hierarchy of evidence. Relevant testimony for this section was provided by: ○ EP8: Practice – Experience of people who use TB services ○ EP12: TB and HIV collaborative commissioning Given the limitations of the evidence available, the adaptations to PH37 recommendations and development of new recommendations were reached on the basis of expert consensus of the committee.

Other considerations	A number of adaptations to the incorporated recommendations were agreed by consensus based on the committees own experience of the system, expertise and based on their discussions of expert testimony to support the benefits described above being realised. In relation to 'who should take action?' the group noted, based on expert testimony, that commissioning support is necessary. Therefore, 'commissioners' was added to first bullet point, along with MDTB teams. The groups agreed that this recommendation should apply to those working with 'people at risk of TB' (replacing hard-to-reach/under-served), no clinical or public health reason was identified to restrict to under-served groups. Recommendations on triage were expanded to include the need to provide everyone with information about TB as part of the triage process, this is based on service user testimony (EP8) who did not feel they receive appropriate information or support during their diagnosis and treatment. In relation to timing of referrals the group considered whether 'within 24 hours' should be changed, initially it was agreed to leave this in, taking in to account for the 7 day hospital system, but subsequently altered to next working day. Further, 'and infection control procedures' was added to this recommendation otherwise the committee considered it to be a risk that infection control procedures may not be followed and it is a core activity that should be carried out rapidly to reduce risk of transmission. The committee also changed the wording to reflect that assessment should also depend on suggestive chest X-rays not just smear positivity otherwise treatment may be delayed inappropriately. The committee discussed there are different types of active TB. From a clinical perspective, all forms require treatment. From a public health perspective, smear-positive, pulmonary TB is the most important as it is responsible for most TB transmissions. This was therefore the specific form of TB that should trigger the most rapid referral processes. As labelled in the recommendations a number of changes have been made to multiple recommendations in this section in many cases this was to make them more relevant to the actual process followed without having to write a pathway. The SDG considered writing separate recommendations describing this process, but decided against this as it may be too prescriptive, and decided that re-ordering some of these actions would clarify what was needed without removing the flexibility needed at a local level. There did not think that the recommendation was incorrect and no change to intent or meaning was undertaken it was simply about supporting implementation. The group discussed the difficulty in defining 'prompt' referral in the recommendation. They noted that while 'prompt' referral would be a two week-wait in cancer services, in TB 'prompt referral' had no meaning. This resulted in the committee agreeing to use the term 'urgent referral' which is an accepted term to mean within 1 week. There was recognition this was quicker than cancer referral times, but also recognised that the person with probable active TB may have had the symptoms for some considerable time prior to being identified as probably having active TB and could have been transmitting TB over this time period and would continue to be a public health transmission risk until they had been diagnosed and treatment had started, necessitating the need for urgent referral. • Recommendation on rapid diagnostics was updated to cross refer to the relevant updated clinical recommendation as a result of the updates on rapid diagnostics by the GDG. A recommendation about outreach was added as this is an important aspect of delivering TB services particularly when attempting to reduce time to diagnosis and to support initiation of treatment and contact tracing activities. The committee expressed concern that without adding detail on MDT-TB teams negotiating with relevant CCGs about payment by tarrif f to fund various referral routes then these referral pathways may not be supported but this was

out of scope for the work.

10.2.23 Recommendations

235. Multidisciplinary TB teams should establish relationships with statutory, community and voluntary organisations that work with people at risk of TB to develop appropriate TB referral pathways. They should ensure these organisations know how to refer people to local TB services. [2012]

236. Multidisciplinary TB teams should accept referrals from healthcare providers and allied organisations working in the community with under-served groups. This includes voluntary and statutory organisations (for example, mobile X-ray teams or community organisations or outreach workers working with vulnerable migrants). [2012]

237. Multidisciplinary TB teams should accept self-referrals to TB clinics by people who suspect they have TB or have recently been in contact with someone with TB. [2012, amended 2015]

238. Multidisciplinary TB teams should consider accepting direct referrals from emergency departments (seerecommendations on Direct referral from emergency departments to multidisciplinary TB teams). [new 2015]

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239. Healthcare professionals should consider urgent referral to TB clinics for people with suspected active TB. They should also ensure the results from first-line diagnostic tests (including a sputum smear and posterior-anterior chest X-ray) are available before the person sees a specialist. (Note: this should not delay the referral.) [2012, amended 2015]

240. Multidisciplinary TB teams should have pathways to triage referrals, start investigations and collect clinical information before the person is seen by a physician. While triaging they should ensure everyone is given information about TB as part of the process (see recommendations on Providing information for the public about TB). This should include who the person should contact if they have any questions and how to access advice or information from support groups, national charities such as TB Alert and other sources such as local government (for example, public health or social care teams). [2015]

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241. Multidisciplinary TB teams should ensure people who have a smear-positive result or imaging features highly suggestive of sputum-smear-positive TB (for example evidence of cavitation on chest X-ray) are assessed the next working day. This is so that case management and infection control procedures start promptly. [2012, amended 2015]

242. The multidisciplinary TB team should assess people who are not sputum-smear-positive but have imaging that suggests pulmonary TB as soon as possible. This should be no later than 5 working days after a referral. [2012, amended 2015]

243. Multidisciplinary TB teams should be able to provide or arrange outreach services to ensure sputum samples or other assessments such as contact investigation can be arranged in the community. [2015]

10.2.24 Rapid-access radiology and other investigation results - referral to multidisciplinary TB team process

10.2.24.1 Evidence to recommendations

Relative value of different outcomes	The committee considered that the priority outcomes supported by these recommendations were reducing time to diagnosis and likelihood of transmission. In addition the secondary outcome of starting treatment more quickly and the associated benefits on reductions in morbidity and mortality associated with TB and late diagnosis and treatment initiation were other important outcomes supported by the recommendations.
Trade-off between benefits and harms	The review and expert testimony (EP4) highlighted the benefit of establishing rapid access radiology processes in managing and controlling TB in a UK setting. The committee noted that the effectiveness review identified this system increased the proportion of cases seen within 14 days (Lynch et al, 2013 & Monk et al 2014), as well as a reduction in time from symptom onset to starting treatment (EP 4 and ES8). Improving referral speed and identifying a local pathway or process for developing and monitoring this was considered a priority to reduce diagnostic delay, time to start of contact tracing activities (thus potential transmissions) and to enable an increased awareness of TB within a number of secondary care settings. The group discussed the evidence described in EP4 and ES2 around nurse led clinics which reinforced the need to have clinician led services. This pathway may also offer an appropriate mechanism for and support the referral route from emergency departments. The harms discussed were the sensitivity and specificity of radiology to identify TB and the knock-on effect of over diagnosis and treatment but believed the benefits outweighed the harms as discussed elsewhere in this guideline.
Trade-off between net health benefits and resource use	The committee recognised this system may have a cost implication and therefore received cost impact evidence to identify a threshold at which the costs would be offset. Based on the evidence for reducing time to diagnosis and potential for reduced transmissions the cost of the process was considered more than justified in the experience of the committee. The group heard evidence on rapid radiology referral. The expert testimony indicated that in terms of resources, a 0.8wte afc band 6 radiology administrator was employed for rapid radiology referral, together with 30 minutes of clinician time per referral. The evidence received showed that rapid referral reduced the time between symptom onset and diagnosis, therefore reducing the time when people are infectious and potentially likely to infect other people with TB. When considering the resources, the group did not believe that 0.8wte administrator time would be required for this post in the majority of places across the UK and as noted below may be particular to the place in which the system had been set-up. Whilst the costs associated with administration in the radiology department was considered a potential opportunity cost, they felt that the costs estimated in the cost impact analysis may have been higher than the true opportunity cost as there are already individuals coding radiology for a variety of disease areas, and felt that the cost impact analysis presented in which this time is absorbed by the system is more reflective of clinical practice across the UK. The group did feel that the additional clinician time needed to assess patients was realistic. Based on the additional clinician time only, the group believed that this cost would easily be off-set by reducing the time when people are infectious and the benefits associated with initiating contact tracing more

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	quickly despite the costs of treating additional cases of TB as these costs were simply brought forward and had further beneficial outcomes of reducing exacerbations of the disease from delays in treatment and the associated morbidity. As such the committee concluded that rapid radiology referral was a highly cost efficient use of resources. They also considered that other rapid referral pathways that reduced the time when people are infectious were also likely to be a cost efficient use of resources. They considered that this intervention was directly associated with reductions in transmissible cases, as they believe that reductions in the time to diagnosis would result in reduced risk of transmission and therefore reductions in incident cases. As the evidence considered showed a reduction in case detection time then the benefits outweighed the resource implications.
Quality of evidence	The evidence used to support changes to this section and specified recommendations includes direct verbal testimony from identified experts with regard to service providers, strategic decision makers, developers or commissioners of services or service users in the field of TB or identified associated fields such as HIV or cancer services. In addition to their verbal testimony provided to the committee in the form of a presentation followed by a question and answer session, experts have also provided written testimony for the committee to reflect upon and for publication as consultation documents. The experts were invited to attend and were provided with committee-led questions and standard forms for written testimony submission based upon the methods described in the manual for the Centre for Public Health Relevant testimony for this section was provided by: ○ EP4: Practice - the Leicester experience including rapid radiology referral model ○ Evidence review – Chapter 4 – Effectiveness review appendix G7 and above: Evidence statement 2: Nurse led service to improve treatment completion in TB patients and reduce costs. King et al 2009 (+). The evidence is directly applicable to the UK. ○ Evidence review – Chapter 4- Effectiveness review appendix G7 and above: Evidence statement 8: Rapid access referral triggered by radiology coding of abnormal chest x-rays can reduce diagnostic delay in TB patients. The evidence was graded at (+) moderate quality and is directly applicable to TB service delivery in the UK, although generalisability of the precise referral process may be limited as described elsewhere in this table whereby, the results may be most applicable to areas of the UK where there is a high incidence of TB or population demographics where substantial populations of high risk people live. ○ Cost impact analysis – Chapter 6: Rapid radiology referral see appendix G7 for further details and threshold analysis results
Other considerations	The group recognised that the primary trigger for rapid referral in this instance was suspicious radiology it therefore focused on recommendations focussed on a rapid radiology referral process, but recognised other clinical areas may benefit from being able to make use of the system. This may also support establishment of the emergency department referral process. However, the group also discussed that the specific area of the UK from which the expert testimony where a rapid radiological referral process had been set-up (EP4) had very particular needs due to the epidemiology of the local population (~ 34% of the local population were born outside the UK according to 2011 census) giving rise to needs that result in potentially higher levels of investment than may be necessary elsewhere. The testimony highlighted that there was a dedicated administrator for the process described in the testimony, which was considered to be somewhat outside the scope of the majority of TB services, but that the task of managing this process may be appropriate for the administration support already recommended for MDTB-teams. Thus, the committee recommended that the

	process be set up to meet the needs of local areas as a one size fits all approach was not warranted. It was clear the system that had been set up was highly individualised to the local needs in Leicester and it was not necessary for everywhere to set up this precise coding and referral system, but this was for local MDTB teams and hospitals to agree based their knowledge of the local population.

10.2.25 Recommendations

244. Local hospitals, clinical commissioning groups and the local multidisciplinary team should consider developing a local pathway for patients with imaging highly suggestive of active TB. The pathway should enable them to be referred by the radiology department by the next working day to multidisciplinary TB teams. Consider including the following in the pathway:

- Agreed standardised radiology codes to identify imaging investigations highly suggestive of active TB.
- Regular liaison between multidisciplinary TB teams and the radiology department (for example weekly) to ensure all patients have been referred to the multidisciplinary team for triage using the agreed local mechanism or pathway. **[new 2015]**

245. Report results of all pathology or other diagnostic results suggesting TB to the multidisciplinary TB team and clinician requesting them. [new 2015]

Update 2015

10.2.26 Direct referral from emergency departments to multidisciplinary TB teams

10.2.26.1 Evidence to recommendations

Relative value of different outcomes	The group considered that reducing diagnostic delay to be the priority outcome for recommending direct referral from emergency departments to multi-disciplinary TB teams, the process was also considered to be of benefit in reducing loss to follow-up in some groups with complex social needs who are also at increased risk of TB. These outcomes were considered highest priority as they would lead to other important outcomes including treatment completion in particular reducing any delay in treatment starting and will have implications for managing risk of transmission all of which will reduce the overall morbidity and mortality associated with TB
Trade-off between benefits and harms	Direct referral from emergency departments to multidisciplinary TB teams was developed following expert testimony on the emergency department practice experience (EP1). The benefits of implementing a direct referral process include the ability to reduce delays in diagnosis but also to reduce loss to follow-up experienced in the groups likely to come into contact with services primarily through emergency departments. The committee were aware of having these referral processes in some places but this was not consistent across the UK and the recommendations would also reduce variation in practice. In addition other testimony (EP8) highlighted that in some instances the knowledge and awareness of staff in an ED setting may have resulted in delayed diagnosis and the attitudes of staff had negatively impacted upon the patient experience in this setting. As a result the committee included recommendations on staff

	training to overcome both of these issues. The harm debated by the group included increased referral rates to TB clinics over-whelming local services, however, given the 50% suspicion to diagnosis yield presented the group considered any potential increase in workload to be more than off-set by the reduced risk of increased morbidity or mortality from delay in diagnosis as well as the reduction in risk of transmission to others. Group agreed it was much higher than the yield of suspicion to diagnosis from GP to MDTB team referrals. Recognising the fact there was no empirical evidence other than an a single audit and their knowledge of the people likely to access services through the emergency department setting the group agreed that a recommendation on monitoring was warranted to enable more systematic audit of implementation of this recommendation for future service delivery assessment and cost effectiveness assessment.
Trade-off between net health benefits and resource use	The group recognised there may be cost implications for creating a pathway and received economic evidence on the cost impact of direct emergency department (ED) referral. In terms of resources, it heard evidence that a small amount of administrator time and clinician time is estimated to be required to enable direct referral from EDs. However, some of this cost can be off-set by diagnosing TB at that ED visit, which could prevent people with TB presenting again in ED with potentially worsened morbidity as a result of the delay in diagnosis and treatment. In terms of outcomes, the committee considered that diagnosing people with TB earlier was likely to reduce the time when they are infective and can potentially pass on TB to other people, which has important health outcomes as well as saved treatment costs. They also recognised that in some cases there would probably be more benefits (e.g. reductions in the complications associated with delayed diagnosis for the individual) than had been considered and the cost impact may have been lower as the benefits were very likely to be under-estimated. As such, it agreed that on economic grounds direct ED referral should be recommended. They felt that this could apply to both urban and rural settings, as although in rural settings there is often a lower rate of TB, there is also more potential for delayed diagnosis resulting from lower level of suspicion for TB in clinicians who do not see the disease presenting as regularly with the knock-on effect of increasing the potential for patients to be presenting in ED several times before the diagnosis of TB is made.
Quality of evidence	As previously noted the committee did recognise the limitations of the evidence they had received and the fact there had been no published comparative evidence on this topic to support their discussions. The recommendations were thus primarily reached on the basis of the expert consensus of the committee. However, even though the evidence received was primarily from expert testimony and from an audit and cost impact analysis based on the testimony and audit data, one of the key reasons for making this recommendation was to reduce variation in practice across the UK and for this reason alone the committee felt compelled to make the recommendations. The applicability and thus generalisability of the evidence received was considered good as they were all from the UK. Relevant testimony for this section was provided by: ○ EP1: Practice - Emergency departments ○ EP8: Practice – Experience of people who use TB services ○ Cost impact analysis – Chapter 7: Direct emergency department referral see appendix G7 for full report and threshold analysis results

Other considerations	The group were surprised about the lack of formal agreements for systematic referral to MDTB teams direct from emergency departments (ED), some members of the committee were aware of agreements in their locality. However, the testimony highlighted this was not always the case. The identified barrier 'lack of a locally agreed pathway' highlighted that without this the ED were not supported in making referrals direct to the TB clinics. The committee expressed concern with this as many under-served groups have no other route into services than via ED. In addition the relatively high yield of 50% suspicion to diagnosis presented in the testimony further supported this as an important setting for high risk groups to receive referral into services. The group recognised the limitation of the testimony only being based on a single audit, however, it was considered compelling enough for the group to agree to make a recommendations about commissioners considering the development of local pathways. EP8 also identified that there may be training needs for emergency care clinicians. This included awareness raising of groups at risk of TB particularly those who are likely to access services via ED (EP1). This is based on the audit which identified there were likely to have been a number of missed opportunities for diagnosis and referral that may have cause delay in diagnosis or even exacerbated the condition or potential for complications and transmissions. This was further supported by EP8 which highlighted that an individual had visited emergency departments multiple times whilst symptomatic but had not been diagnosed or referred increasing risk of transmission given their living circumstances (EP8). Additionally EP8 also identified there may be training needs within emergency departments around the type of advice and guidance some groups (in this case street drinkers) may need regarding TB, as well as the need to ensure non-judgemental language is used to support these people to engage with services not only for their own health but also as a means to reduce transmission when a communicable disease is suspected. EP8 evidenced prejudice from healthcare staff, and lack of explanation of treatment including side effects

10.2.27 Recommendations

246. Commissioners and multidisciplinary teams should consider working with emergency departments to develop direct referral pathways for people with suspected TB so that:

- the local multidisciplinary team is informed of all suspected cases of TB using the appropriate process
- referral is accepted from any appropriate healthcare professional, for example an on-call radiologist. **[new 2015]**

247. Emergency department clinicians should ensure first-line diagnostic tests for TB are performed (see table 1 in recommendation 33). [new 2015]

248. Emergency departments should consider carrying out audits of their direct referrals because of suspected TB and the outcomes of diagnosis. [new 2015]

249. Multidisciplinary TB teams should consider training emergency department staff in:

- using approaches that do not stigmatise people with TB
- giving people with TB appropriate advice. **[new 2015]**

10.2.28 Research recommendations

17. Referral mechanisms and their impact on reducing time to diagnosis

Are rapid radiological referral and direct referral from emergency departments effective and cost effective at reducing time to diagnosis and diagnostic uptake compared to current practice.

Why this is important

The GDG consider time to diagnosis a key outcome in managing TB prevention and control both in terms of outcomes for the person affected but also in reducing transmission risk to the general population. There was some strong evidence available on the effectiveness of a rapid referral process in one area of the UK but as the population served has a particular epidemiology this created some uncertainty when extrapolating this evidence to the population as a whole, other than audit data there there was no empirical evidence for emergency department referral but given the part of the health services contact with certain high risk groups who may not have a GP this mechanism needs further evaluation. Furthermore, neither process had cost-effectiveness evaluations available.

Update 2015

10.2.29 Identifying and managing active TB in prisons or immigration removal centres: organisational factors

10.2.29.1 Evidence to recommendations

Relative value of different outcomes	The group agreed that reducing transmission of TB and delays in diagnosis were the outcomes considered of highest priority in adding custody suites to this set of recommendations incorporated from PH37; with the knock-on effect of reducing both morbidity and potential mortality associated with TB.
Trade-off between benefits and harms	The group agreed that recommendation 8 relating to identifying and managing active TB in prisons or immigration removal centres could be incorporated in the service delivery guidance. They discussed and agreed to add custody suites as an additional place where risk of transmission was increased as in some custody suites detainees had to share cells. In addition it was agreed that some people at greater risk of having TB may be more likely to come into contact with custody suite personnel and thus there was also a potential to identify undiagnosed cases of TB. The benefits of adding custody suites was the ability to identify undiagnosed cases of TB so that treatment could begin and to reduce the risk of transmitting TB to fellow detainees or staff. The group discussed potential risk and agreed that treatment relapse due to a lack of continuity of care may be an issue, however, they agreed that given the co-ordination and joint working provided by both the multi-disciplinary TB team then as long as this relationship was working effectively then should the detainee move into to prison or back into the community then this would not be an issue as the MDTB team could maintain contact once the case was diagnosed.
Trade-off between net health benefits and resource use	The group recognised this may require additional training for custody suite staff but considered this was of low cost for the potential health benefits. Whilst there may be a cost associated with identifying and treating additional cases to the MDTB team, as noted previously as the committee expected all cases to be identified then earlier id/treat was preferable given the risk of

	transmission or increased risk of complications associated with later diagnosis, this would be cost saving.
Quality of evidence	No evidence was received on this extrapolation this was a change based on committee consensus alone.

10.2.301 Recommendations

250. Multidisciplinary TB teams, prisons, custody suites and immigration removal centre healthcare services should have named TB liaison leads to ensure they can communicate effectively with each other. [2012, amended 2015]

251. Prison, custody suites and immigration removal centre healthcare services should develop a TB policy by working with the TB control board and multidisciplinary TB team and the local Public Health England health protection team. [2012, amended 2015]

252. Multidisciplinary TB teams, in conjunction with prisons, custody suites and immigration removal centre healthcare services, should agree a care pathway for TB. This is to ensure that any suspected or confirmed cases are reported to, and managed by, the multidisciplinary TB team. [2012, amended 2015]

253. Multidisciplinary TB teams, in liaison with prisons, custody suites or immigration removal centre healthcare providers, should manage all cases of active TB. Investigations and follow-up should be undertaken within the prison or immigration removal centre if possible. [2012, amended 2015]

10.2.317 Accommodation during treatment

10.2.31.18 Evidence to recommendations

Relative value of different outcomes	The group considered that the priority outcome this recommendation supports is increasing treatment completion, although the control of risk and rates of transmission is an important secondary outcome along with the knock on impacts on morbidity and mortality associated with TB.
Trade-off between benefits and harms	The group agreed that recommendations on 'accommodation during treatment' from PH37 should be incorporated into the service delivery guidance. The group agreed that the overall benefit of these recommendations were that some people particularly those with complex social needs often needed accommodation to ensure they completed their treatment. Additionally many professionals who can support identification and availability of housing solutions were not aware of the risk of TB and MDR-TB. In particular some of the core national organisations who may aid information and training development and delivery had not been captured. The harm associated with not finding accommodation for those at most need was that this group was particularly at risk of not only treatment failure and the potential for MDR-TB to develop but also given their housing circumstances they were also likely to stay in settings associated with crowding such as hostels or unregulated houses of multiple occupation. This therefore had significant risk for others.
Trade-off between net health benefits	There has been no change to the intent or meaning of recommendations incorporated from PH37. The Group believed that the majority of people with TB would be eligible for state-funded accommodation if they were able to

and resource use	navigate the housing system. Given the results of the economic modelling and analysis in PH37, the group agreed that providing accommodation was preferable to the existing alternatives (for example, bed blocking in hospitals or being lost to follow-up), which would increase resource use. They considered from their expert perspectives that the health benefits outweighed the costs of implementing these recommendations, and consider training and awareness raising as an absorbable cost through the continuing professional development of any workforce.
Quality of evidence	No high quality comparative evidence was available to support the changes made by the committee to the incorporated recommendations, evidence was provided through expert opinion which the committee recognise is the considered the lowest quality on the 'hierarchy of evidence' given the potential biases in this form of evidence. However, as noted above given the changes made and the expert considerations of the committee this was not seen as a barrier to adding to these recommendations. Relevant testimony for this section was provided through 'EP9: Accommodation, housing and TB'. Additionally, as the examples provided in the testimony were all from UK practice then the group considered it to be particularly applicable to their deliberations. Given the limitations of the evidence available, the recommendations were reached on the basis of expert consensus by the committee.
Other considerations	The aim of the new recommendations was to support the awareness raising recommendations made elsewhere in this guideline and to raise awareness specifically in groups of professionals who may be able to support the successful and more systematic implementation of previous recommendations from Public Health Guideline 37. The testimony highlighted that there were a number of levers not included in the previous recommendations that may support implementation and a number of groups who were not included who could offer support to enable these recommendations to be delivered. There are examples of good practice where housing has been provided to enable TB treatment, but it was noted that it was currently too early to offer directly attributable outcomes measures as the implementation of PH37 recommendations on accommodation is far from systematic. The issues highlighted in the expert testimony that may reduce implementation include the lack of information available and awareness of TB in the wider non-health/public health workforce who can support this guidance. The committee therefore agreed that the previous recommendation had not captured some of the core organisations who may aid information, training development and delivery had not been captured. They added recommendations to overcome this. In addition to the testimony the committee reflected on their experiences of supporting TB service delivery around housing issues and discussed a number of adaptations to the incorporated recommendations to improve clarity. The group added an additional actor to work on developing the process for identifying accommodation for people with TB 'hospital discharge teams', this was to further improve support for reducing the potential for bed blocking one of the cost implications noted above. The group discussed whether they could be more prescriptive about who is responsible for providing funding for accommodation to support treatment completion. They agreed that whilst it was a commissioning decision it was a local issue therefore the primary local commissioners (local government and clinical commissioning groups) should be actioned with this recommendation. They also considered the testimony about the changes to the Care Act 2014 offering leverage to implementation and agreed to add this to the recommendation to ensure commissioner recognised this as an important

consideration when making these decisions.

No other changes were made other than to reflect who should take action, and who would benefit from the recommendation as incorporation from a different template lost this detail and the group considered this an important aspect of the recommendations. Based on the testimony and committee discussions about their experience of working with these groups agreeing accommodation a recommendation has been added to improve awareness of and partnership working with those organisations who can have a national influence on raising awareness within their membership of the needs of people with TB.

It was recognised by the group both due to personal experience but also from the testimony that there was often a dearth of data and viable information available locally and they would have liked to address this. However, they recognised that this may need to be underpinned by some more formal research on the area of housing and TB including empirical and qualitative outcomes of the provision of housing and/or provision of information on the kind of data and knowledge needed locally to aid implementation of the recommendations

10.2.321 Recommendations

254. Multidisciplinary TB teams should assess the living circumstances of people with TB. Where there is a housing need they should work with allied agencies to ensure that all those who are entitled to state-funded accommodation receive it as early as possible during their treatment. [2012]

255. Multidisciplinary TB teams, commissioners, local authority housing lead officers and other social landlords, providers of hostel accommodation, hospital discharge teams, Public Health England and the Local Government Association should work together to agree a process for identifying and providing accommodation for homeless people diagnosed with active pulmonary TB who are otherwise ineligible for state-funded accommodation. This includes people who are not sleeping rough but do not have access to housing or recourse to public funds. The process should detail the person's eligibility and ensure they are given accommodation for the duration of their TB treatment. [2012, amended 2015]

256. Local Government and clinical commissioning groups should fund accommodation for homeless people diagnosed with active TB who are otherwise ineligible for state-funded accommodation. Use health and public health resources, in line with the Care Act 2014. [2012, amended 2015]

257. Multidisciplinary TB teams should make people who would not otherwise be entitled to state-funded accommodation aware that they may lose this accommodation if they do not comply with treatment. They should ensure plans are made to continue housing people once their TB treatment is completed. [2012]

258. Public Health England, working with the Local Government Association and their special interest groups, should consider working with national housing organisations such as the Chartered Institute of Housing and the National Housing Federation to raise the profile of TB. This is to ensure people with TB are considered a priority for housing. Consider developing and delivering training on TB and the need for housing support for their members. [new 2015]

Update 2015

1

11 Active case finding

11.1 Overview

11.1.1 Clinical introduction

Active case finding is looking systematically for cases of active tuberculosis and latent infection in groups known, or thought to be, at higher risk of tuberculosis, rather than waiting for people to develop symptoms/signs of active disease and present themselves for medical attention (passive case finding). Active case finding is informed by a knowledge of the general epidemiology of TB in the country, and in population subgroups. The current incidence of active TB in England and Wales is 12.9 cases per 100,000 population per year, with individual ethnic groups having rates of 4 per 100,000 (white), 104 per 100,000 (Indian), 145 per 100,000 (Pakistani), and 211 per 100,000 (black African).{140} Data are not available on latent tuberculosis rates in the general population. Active case finding, if targeted on appropriate groups, or subgroups, should have a yield substantially above that that would be found by chance screening. The Chief Medical Officer's TB Action Plan{2} set improvements in case finding as one of the essential activities to improve TB care in England and Wales, and to reverse the trend of increasing incidence.

11.1.2 Current practice

The review of current services included service provision and organisation for active case finding in terms of contact tracing (sections 12.2 and 12.3), new entrant screening (section 11.7), and screening other risk groups.

Outside London, 25% of service providers had some screening for high-risk groups, whereas within London, 39% had such screening. Examples of high-risk groups were drug users, the homeless and alcoholics.

11.2 Contact tracing: human-to-human transmission

11.2.1 Clinical introduction

Contact tracing and examination have traditionally been undertaken to find associated cases, to detect people infected but without evidence of disease (latent infection) and to identify those not infected and for whom BCG vaccination may be appropriate. Where recent infection has occurred (e.g. clinical disease in children), contact tracing is done to find a source of infection, and any co-primary cases. In people with latent tuberculosis, BCG vaccination does not prevent its development into active disease. BCG vaccination is addressed in chapter 10 of this guideline.

Five contact studies in England and Wales,{306–310} reporting 22,971 contacts in the early 1990s, showed that up to 10% of new TB cases were diagnosed through contact tracing, that disease occurred in about 1% of contacts, and that disease was usually found on the first visit in unvaccinated contacts of sputum smear-positive disease. Three smaller studies reported in the late 1990s in England and Wales,{311–313} largely confined to close contacts, showed a mean number of contacts examined at 6.5 per index case, and confirmed a secondary case yield of 1% (1,000/100,000).

Smear-negative pulmonary tuberculosis is significantly less infectious than smear-positive, but some transmission does occur. Studies in San Francisco{314} and Western Canada{315} using DNA fingerprinting estimated this transmission risk (as a proportion of smear-positive transmission risk) at between 0.22 and 0.18–0.35 respectively, similar to estimates (0.28) using 'conventional' methods.{316} DNA fingerprinting studies may also identify clusters not

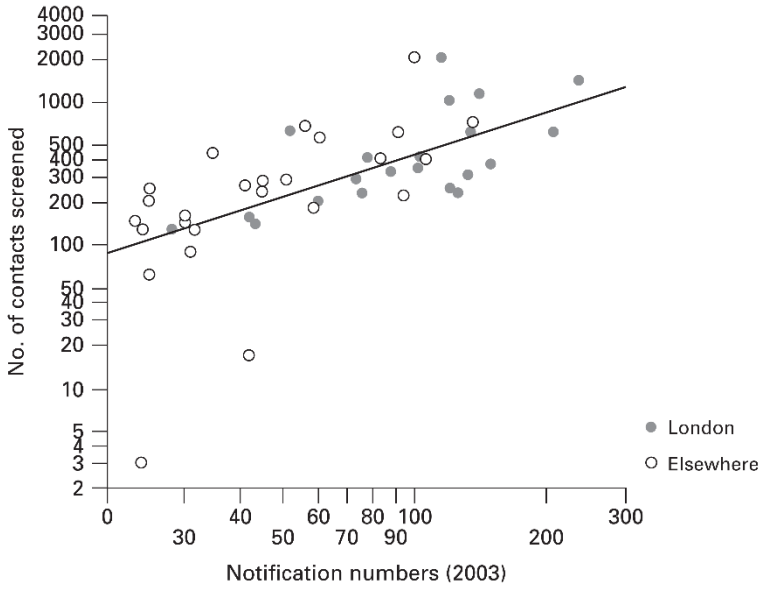
identified by 'conventional' contact tracing and in some cases assumed to be recently linked.{314},{315}

11.2.2 Current practice

The review of current services found that outside London, 70% of service providers had contact clinics and 16% saw patients at home. Within London, 91% had a contact tracing clinic, and no service providers saw patients at home other than in exceptional cases.

An assessment of the extent of current contact tracing practice can be made by comparing the number of notified cases with the number of contacts screened. The graph below, where each dot represents a service provider, and clinics which only do tracing have been removed, shows that there is considerable variation in the number of contacts traced per index case. (Perfect consistency, which is an unreasonable expectation, would be demonstrated in a straight line.)

Figure 2: Correlation of contacts screened with cases notified (logarithmic scale)



A similar comparison has been made between the number of contacts traced and the number of treatments for latent TB infection cases, and is reported under section 10.1.

11.2.3 Methodological introduction

Two clinical questions were drawn up to search the evidence base for this topic. The results of the searches and the critical appraisal are discussed below for each in turn.

Are contact tracing procedures effective in identifying cases of tuberculosis disease or infection (excluding contacts of cattle with TB)?

No systematic reviews or randomised controlled trials were found that met the inclusion criteria for this question.

The literature search identified 10 studies conducted in England and Wales that reported epidemiological descriptions of specific contact tracing exercises. These studies did not include comparative case yield data from other contact tracing or case finding exercises in similar populations and settings, and so were not considered for appraisal. Without comparative data, these studies could not evaluate the effectiveness of the specific contact tracing intervention method used. Nevertheless these studies contribute towards an epidemiological overview of contact tracing in England and Wales, and the main results of

1 these studies are collated in Table 36 below in order to provide local background information
2 on this aspect of active case finding.

3 **Table 36: Descriptive studies of contact tracing carried out in England and Wales**

Reference	Description	Results
Ruddy MC, Davies AP, Yates MD, Yates S *et al*. Outbreak of isoniazid resistant tuberculosis in north London. *Thorax* 2004;**59(4)**:279–285.	Study type: descriptive. Population: contact tracing of isoniazid resistant TB outbreak in North London, including prisons. Study period: retrospective analysis 1995–2001.	• At least 440 named close contacts of confirmed or probable TB cases to date. • Screening of 269 close contacts yielded 13 confirmed or probable TB cases, 13 clinical cases, and three linked cases. • This represents a transmission rate of 11% among close contacts screened to date. • 27 infected contacts were placed on treatment for latent TB infection.
Corless JA, Stockton PA, Davies PD. Mycobacterial culture results of smear-positive patients with suspected pulmonary tuberculosis in Liverpool. *European Respiratory Journal* 2000;**16**:976–979.	Study type: descriptive. Population: contact tracing of suspected pulmonary TB from two hospitals in Liverpool. Study period: retrospective analysis 1996–1999.	• A total of 937 contacts were identified from 57 index patients with cultured *M. tuberculosis*. • No contact in the study developed tuberculosis while under surveillance.
Ansari S, Thomas S, Campbell IA, Furness L, Evans MR. Refined tuberculosis contact tracing in a low incidence area. *Respiratory Medicine* 1998;**92(9)**:1127–1131.	Study type: descriptive. Population: patients with TB and their contacts in South Glamorgan. Study period: retrospective analysis 1992–1994.	• A total of 726 contacts were identified from 103 index patients, with 707 contacts receiving full screening. • TB disease was found in 7 (1%) close contacts, all identified at the initial screening (one with smear-positive index case; five with two overseas index cases with unknown smear status; one with child index case with unknown smear status). • TB disease was found later in a further five contacts initially screened and cleared (in two cases the protocol was not followed correctly and three cases developed extra- pulmonary TB. • Treatment for latent TB infection was given to 21 (2.9%) of close contacts.
Irish C, Jolly E, Baker T. Contact tracing smear	Study type: descriptive epidemiological study. Population:	• One of 158 (0.5%) contacts of POS cases,

Reference	Description	Results
positive and non-pulmonary tuberculosis in a high incidence area. *Thorax* 1997;**52**:A34.	contacts of non-pulmonary (NP), sputum smear-positive (POS), and negative (NEG) cases of tuberculosis disease in Tower Hamlets. Study period: 1995.	four of 196 (2%) contacts of NEG cases, and none of 57 contacts of NP cases were treated for tuberculosis disease. • Twenty-two of 158 (14%) POS contacts, 21 of 196 (11%) NEG contacts, and five of 57 (9%) NP contacts received treatment for latent TB infection. • Differences in proportions of POS, NEG, and NP contacts requiring one or more repeat X-ray, further clinic follow-up, treatment for latent TB infection or full tuberculosis treatment were not significant.
Stoddart H, Noah N. Usefulness of screening large numbers of contacts for tuberculosis: questionnaire-based review. *British Medical Journal* 1997;**315**:651.	Study type: cross-sectional survey Population: 155 districts in England and Wales where in the preceding three years more than 100 contacts were screened in response to specific incidents. Study period: April 1994.	• Forty-four cases of tuberculosis disease were found in 18 of the 56 investigations, giving a detection rate of 0.375%. • A further 106 (0.9%) contacts received treatment for latent TB infection. • The development of tuberculosis in 39 investigations with details available was significantly correlated with the proportion of contacts who had tuberculin skin test positive results (P=0.008).
Harding MJ, Pilkington P, Thomas J. Tuberculosis epidemiology in Croydon. *Public Health* 1995;**109**:251–7.	Study type: descriptive. Population: contact tracing in response to tuberculosis incidents in Croydon. Study period: retrospective analysis 1988–1991.	• A total of 522 close contacts were identified from 172 index cases. • Three cases of tuberculosis were identified from the contacts (0.6%). • Forty-eight contacts (9.2%) had either a positive Heaf test or chest X-ray indicative of past primary infection. • 19.6% of contacts of index patients with smear-positive disease were 'positive' *vs.* 9.8% of contacts of non-smear positive index patients, *vs.* 5.2% of patients with non-pulmonary disease (P=0.0002).

Reference	Description	Results
Hardinge FM, Black M, Chamberlain P. TB contact tracing in South Buckinghamshire from 1994 to mid 1998. *Am J Respir Crit Care Med* 1999;**159**:A303.	Study type: descriptive. Population: all patients with TB and their contacts in South Buckinghamshire. Study period: retrospective analysis 1994 to mid 1998.	• 369 contacts were identified from 72 index cases. • Eight cases of TB were identified among contacts, four at initial screening (1%) – all were close contacts of smear-positive pulmonary disease index cases. • Three contacts were given treatment for latent TB infection (0.8%), and 143 (38%) were given BCG vaccination.
Ormerod LP. Results of tuberculosis contact tracing: Blackburn 1982–90. *Respiratory Medicine.* 1993;**87**:127–131.	Study type: descriptive. Population. contact tracing in Blackburn using methods 'virtually identical' to procedures recommended in 1983 by the JTC. Study period: retrospective analysis 1982–1990.	• 7,017 close contacts were identified from 649 index cases. • 50 cases of TB (0.7% of all contacts) were identified, 13 in the white ethnic group, and 37 in the Asian ethnic group. • 38% of cases in the Indian subcontinent ethnic group were contacts of smear-positive pulmonary disease, and 46% were contacts of other forms of respiratory disease. • All cases of TB were in white contacts of index cases with smear-positive pulmonary disease.
Kumar S, Innes JA, Skinner C. Yield from tuberculosis contact tracing in Birmingham. *Thorax* 1992;**47**:875.	Study type: descriptive. Population: yield from contact tracing of notified TB cases at the Birmingham chest clinic using a contact tracing procedure 'broadly similar' to 1990 BTS guidelines. Study period: retrospective analysis 1987–1989.	• 7,960 contacts were identified from 788 index cases. • 75 new cases of TB were identified from contacts (1% of all contacts), 46 of Indian subcontinent origin, 15 white, and 14 black Caribbean. • 254 contacts were given treatment for latent TB infection (3% of all contacts). • All contacts with TB disease were contacts of index cases with pulmonary smear- positive TB except for six (8% of total) Indian contacts of index cases with non-respiratory disease.
Hussain SF, Watura R, Cashman B, Campbell IA,	Study type: descriptive. Population: TB contact tracing in South	• 611 contacts were identified from 101 index

Reference	Description	Results
Evans MR. Audit of a tuberculosis contact tracing clinic. *BMJ.* 1992;**304**:1213–15.	Glamorgan. All patients with a diagnosis of active TB disease who appeared in the contact tracing records and laboratory data from the Public Health Laboratory Service (PHLS) *Mycobacterium* Reference Unit within this period were included in the study, as were all recorded contacts of these patients. Study period: retrospective analysis 1987–89.	patients. • Active TB disease was diagnosed in five contacts (two of Indian subcontinent origin, three of other origins), all made on initial screening. All were close contacts and none were known to have been vaccinated. • Four contacts who received treatment for latent TB infection were also close contacts of patients with smear-positive pulmonary TB and had not been vaccinated.
Teale C, Cundall DB, Pearson SB. Time of development of tuberculosis in contacts. *Respiratory Medicine* 1991;**85**:475–7.	Study type: descriptive. Population: contact tracing procedures at the Leeds chest clinic Study period: retrospective analysis 1983–1987.	• 6,602 contacts were identified from 555 notified index cases. • 42 (8%) contacts had TB disease (10 cases smear or culture positive, five contacts of Asian origin, five contacts of non-family members; four cases diagnosed more than one year after first clinic attendance). • 35 (6%) previously unimmunized child contacts with Heaf grade 2 or more results received treatment for latent TB infection.

Of the 17 studies appraised, 11 were excluded due to methodological limitations, which are presented in Appendix I. Six non-analytic studies were included as evidence in two main areas:

- non-homeless and homeless populations
- contact tracing and DNA fingerprinting analysis.

Are contact tracing procedures which identify casual contacts in addition to close contacts effective in identifying cases of tuberculosis disease or infection?

Studies were included that compared the number of cases of latent tuberculosis infection and/or active tuberculosis disease identified during contact tracing in groups of close and casual contacts. No systematic reviews, randomised controlled trials, cohort or case control studies were found that met the inclusion criteria for this question.

Seven studies on contact tracing in close and casual contacts were identified, but six of these{316–321} were excluded due to methodological limitations presented in Appendix K. One prospective non-analytic study {322} was included as level 3 evidence for this question.

11.2.41 Evidence statements

2 Contact tracing compared in non-homeless and homeless populations

3 A study carried out in the USA{323} found that contact tracing identified significantly more
4 contacts in non-homeless compared to homeless tuberculosis cases. The evidence is
5 presented in Table 37.

6 **Table 37: Summary of evidence: contact tracing in homeless and non-homeless**
7 **people**

Outcome	Results Homeless *vs.* non-homeless TB index cases	Statistical significance	NICE grade
Mean number contacts identified	2.7 *vs.* 4.8	p<0.001	3+
Four plus contacts identified	40 (26) *vs.* 1419 (50)	p<0.0001	3+
No contacts identified N (%)	70 (46) *vs.* 304 (11)	p<0.0001	3+

8 Contact tracing and DNA fingerprint analysis

9 Five non-analytic studies compared DNA fingerprint analysis of transmission links between
10 cases of tuberculosis with the number of epidemiological links established through contact
11 tracing for the same set of cases. These studies did not have a control group. Factors for
12 consideration within this topic are used below.

13 • DNA fingerprint analysis can only be carried out on culture-positive cases of *M.*
14 *tuberculosis*. Contact tracing includes culture-positive and-negative cases, and identifies
15 cases of latent infection. Contact tracing therefore covers a wider population of at-risk
16 contacts than DNA fingerprinting analysis, so the procedures are not equivalent
17 comparators.

18 • Reliance on *M. tuberculosis* isolates means that molecular typing usually occurs some
19 time after contact tracing has commenced, and so cannot complement in real time the
20 epidemiological links established by the latter.

21 • None of the studies were carried out in the United Kingdom.

22 • Contact tracing was generally poorly reported and differed within each study setting.

23 Four studies{324–327} found that when contact tracing and DNA fingerprint analysis were
24 carried out on the same group of contacts, tracing found fewer transmission links between
25 identified cases of active tuberculosis than DNA fingerprint analysis. The evidence from the
26 studies is presented in Table 38 below.

27 **Table 38: Summary of evidence: DNA fingerprinting**

Results: DNA fingerprint analysis	Results: Contact tracing	Ref and NICE grade
155 clustered TB cases	Identified links in 37/155 (24%) clustered cases; missed detectable links in 10/155 (6%) clustered cases; non-detectable (by contact tracing) links in 106/155 (68%) clustered cases.	{324} 3+
Four clusters of TB cases with transmission links identified	Identified links in 3/4 (75%) clusters.	{325} 3+
84 TB cases in 26 clusters	Identified links in 20/84 (24%) linked TB cases.	{326} 3+
96 TB cases in eight	Two TB cases identified an unspecified number of cases	{327} 3+

Results: DNA fingerprint analysis	Results: Contact tracing	Ref and NICE grade
clusters	in the same cluster as 'contacts'.	

One study{328} found that DNA fingerprint analysis identified erroneous transmission links inferred by contact tracing to exist between cases of tuberculosis disease.

Eight of 13 epidemiological transmission links (61.5%) identified by contact tracing were verified by DNA fingerprint analysis, but the remaining five (38.5%) cases linked by contact tracing did not acquire their infection from the putative source. (**3+**)

Close contacts compared to casual contacts in detecting latent tuberculosis infection

One study{322} found that both latent tuberculous infection and active tuberculous case yields were significantly higher for close compared to casual contacts of 302 index cases diagnosed at a single non-hospital practice. The evidence is summarised in Table 39 below.

Table 39: Summary of evidence: contact tracing in close and casual contacts

Outcomes	Close contacts N (%)	Casual contacts N (%)	Association/statistical significance (OR)	NICE grade
Latent TB infection	488 (55.9)	94 (26.4)	OR 3.54 (95%CI 2.68 to 4.69 p<0.00001)	3+
Active TB disease	40 (4.6)	2 (0.6)	OR 8.51 (95%CI 2.18 to 73 p<0.001)	3+

11.2.5 From evidence to recommendations

General issues

Contact tracing procedures should be carried out on a patient-centred basis. The GDG felt it was important to consider the lifestyle of an index/source case carefully as it may reveal places of close contact other than domestic or occupational such as homeless shelters, cinemas, bars, clubs, prisons or aircraft.{329}

Contact tracing is usually conducted according to the 'stone in the pond' principle,{330} and it is with this in mind that the recommendations below are set out. Closest contacts (those with most exposure, typically household contacts) are found and assessed first. If sufficient TB is found to raise clinical suspicion of further infection, another tier of contacts are traced, and so on. This helps to limit the effort put into such exercises.

Definition of close contacts

Descriptive studies from the UK which were considered by the GDG do not give a clear definition of close contacts and it is therefore difficult to give guidance on whom to trace.

It would be useful to give TB nurses an objective definition of close contacts, but there is insufficient evidence to make a recommendation on factors such as length of time spent in the same room without ventilation before 'close contact' is deemed to have occurred.

DNA fingerprint analysis

DNA 'fingerprint' analysis has been used to identify clusters that have not been identified by contact tracing. It can support the presumed links between cases.

Only one study checked the effectiveness of molecular typing through follow-up, and the GDG did not feel that the evidence base was sufficient to inform clinical recommendations.

Molecular typing will underestimate the epidemiological linkages relevant to contact tracing, because it relies exclusively on analysis of culture-positive TB isolates.

Who to include in contact tracing?

Whilst the highest pick-up will be in the contacts of pulmonary smear-positive cases, there is a significant yield from screening household contacts even of extrapulmonary index cases, as this is assessing and screening a local population with a high incidence of TB.

Contacts with a cumulative total exposure to a smear positive case of TB exceeding eight hours within a restricted area equivalent to a domestic room are equivalent to domestic contacts; the guideline recommends tracing these contacts in addition to the domestic ones.

'Inform and advise' information is an important minimum level of TB education for all contacts once they are traced. However, for close contacts, this should not pre-empt screening and discussion with a healthcare professional (as a normal part of contact tracing), because of patient confidentiality.

11.2.6 Recommendations

259. Once a person has been diagnosed with active TB, the diagnosing physician should inform relevant colleagues so that the need for contact tracing can be assessed without delay. Contact tracing should not be delayed until notification. [2006]

260. Offer screening to the household contacts of any person with pulmonary TB[nn]. Household contacts are defined as those who share a bedroom, kitchen, bathroom or sitting room with the index case. [2006, amended 2015]

261. Assess symptomatic household contacts for active TB. [new 2015] Update 2015

262. In asymptomatic household contacts younger than 65 years[oo], consider standard testing for latent TB, followed by consideration of BCG (see section 1.1.3) or treatment for latent TB infection (see section 1.2.2) once active TB has been ruled out (see section 1.3.1) for people who:

- are previously unvaccinated, and
- are household contacts of a person with sputum-smear-positive TB, and
- are Mantoux negative (see section 1.2.1). **[2006, amended 2015]**

263. In asymptomatic household contacts older than 65 years[pp], consider a posterior-anterior chest X-ray (if there are no contraindications), possibly leading to further investigation for active TB. [2006, amended 2015]

[nn] The Committee has revised this recommendation – which previously referred to 'all people with active TB' – to limit testing to contacts of people with potentially infectious TB.

[oo] The upper age limit for offering testing to diagnose latent TB was previously 35 years, but has been increased to 65 years. Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years. Therefore, it is necessary to update this recommendation to reflect the revised upper age-limit for treatment..

[pp] The upper age limit for offering testing to diagnose latent TB was previously 35 years, but has been increased to 65 years. Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of

264. For people with pulmonary TB, assess other close contacts. These may include boyfriends or girlfriends and frequent visitors to the home of the index case. Occasionally, a workplace associate may be judged to have had contact equivalent to that of household contacts, and should be assessed in the same way. [2006, amended 2015]

265. Do not routinely assess casual contacts of people with TB, who will include most workplace contacts. [2006, amended 2015]

266. Assess the need for tracing casual contacts of people with pulmonary TB[qq] if:

- the index case is judged to be particularly infectious (for example, evidenced by transmission to close contacts), or
- any casual contacts are known to possess features that put them at high risk of going on to develop active TB. **[2006, amended 2015]**

267. Offer 'inform and advise' information to all contacts of people with smear-positive TB. [2006]

treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years. Therefore, it is necessary to update this recommendation to reflect the revised upper age-limit for treatment..

[qq] The Committee has revised this recommendation – which previously referred to 'all people with active TB' – to limit testing to contacts of people with potentially infectious TB.

11.3 Contact tracing: cases on aircraft

11.3.1 Clinical introduction

The evidence base upon which assessments can be made of the risks of transmission of TB in aircraft is relatively slim. The confined space and the recirculation of air clearly give rise to potential hazards. Whether or not these are greater for an individual on a single flight than, say, regular travel on the same commuter bus or train as an infectious case of TB cannot be established.

Aircraft passengers are, in theory at least, more readily identifiable than passengers of other kinds. Identifiability and traceability are not, however, synonymous and characteristically, aircraft passengers do not make multiple repeat journeys and are widely dispersed once they reach their destination. Further, airlines (who hold the passenger lists) may prove reluctant to disseminate information about the hazards of having travelled with them.

Recommendations about contact tracing where an aircraft passenger has been identified as having infectious TB must therefore be guided by the practicalities of the process.

11.3.2 Methodological introduction

Studies were targeted that attempted to establish whether latent tuberculosis infection and active tuberculosis disease identified by contact tracing in passenger and crew contacts was due to recent transmission from an index case of tuberculosis on an aircraft. No systematic reviews, randomised controlled trials, or case control studies were found that met the inclusion criteria.

One cohort study conducted in the USA{334} compared case yields for latent tuberculosis infection identified by contact tracing in flight crew exposed to an index case of tuberculosis with flight crew with no prior exposure to infectious tuberculosis. Five non-analytic studies{335–339} were identified that investigated whether latent tuberculosis infection identified in passenger and crew contacts was due to prior risk factors for tuberculosis or recent exposure to an index case of tuberculosis on an aircraft. Methodologically, all six studies differed with regard to:

- varying geographical locations
- varying countries of residence of contacts
- differing exposure periods
- variation in prior BCG vaccination of contacts depending on country of residence
- sample sizes ranging from 100 to 760.

Prior risk factors for latent tuberculosis infection and contamination of tuberculin skin test results identified in the study populations included:

- high BCG vaccination rates
- prior exposure to family members or close friends with tuberculosis
- born or resident in a country with a high incidence of tuberculosis
- extensive travel in settings with a high incidence of tuberculosis
- having old, inactive tuberculosis
- exposure to tuberculosis in the workplace (excludes flight crew)
- exposure to other mycobacterial infection.

11.3.31 Evidence statements

2 Recent transmission of latent tuberculosis infection

3 One study {334} found significantly more cases of recent transmission of tuberculosis
4 infection in aircraft crew exposed to an index case of tuberculosis than in a control group of
5 non-exposed crew. Two studies{336},{337} found evidence of recent transmission of TB
6 infection in airplane contacts of cases with tuberculosis disease, while three other
7 studies{335},{338},{339} found no conclusive evidence of recent transmission in airplane
8 contacts of active TB disease cases. None of the studies reported symptoms of active
9 tuberculosis in contacts. The evidence is presented in Table 40 and Table 41 below.

10 **Table 40: Exposed and non-exposed aircraft crew**

N (%) exposure group Mantoux test positive	N (%) control group Mantoux test positive	Association/statistical significance	Ref and NICE grade
May–July 1993: 10/169; 5.9	**May–July 1993:** 13/247; 5.3	NS	{334} 2++
August–October 1993: 13/43; 30 (Mantoux test positive rates ≥5 mm induration)	**August–October 1993:** 13/247; 5.3 (Mantoux test positive rates ≥5 mm induration)	RR 5.74 (95%CI 2.86 to 11.54, p<0.01)	
11/43; 25.6 (Mantoux test positive of 10 mm induration)	4/247; 1.6 Mantoux test positive (rates of 10 mm induration)	RR 15.8 (95%CI rates 5.27 to 47.34, p<0.01)	

11 **Table 41: Aircraft contacts with latent TB infection attributed to prior risk factors vs.**
12 **aircraft-mediated transmission**

N (%) Mantoux test positive contacts with prior risk factors for TB	N (%) Mantoux test positive contacts attributed to aircraft transmission	Ref and NICE grade
6/9 (66.6)	3/9 (33.3) Flight exposure-related conversion rate for latent TB infection was 1.3% (3/225 contacts)	{336} 3+
14/20 (70%)	6/20 (30) Flight exposure related conversion rate for latent TB infection was 0.8% (6/760 contacts)	{337} 3+
24/24 (100%)	0	{335} 3+
32/34 (94%)	2/34 (5.8) Impossible to determine whether two US-born Mantoux test positive reactors were due to aircraft transmission, since estimated 4–6% of the US population are Mantoux test positive	{338} 3+
5/5 (100%)	0	{339} 3+

13 **Duration of exposure**

14 One study{334} found that duration of exposure to the index case was the factor most
15 strongly associated with latent tuberculosis infection among exposed aircraft crew contacts.

16 Over three months 49 (96%) crew contacts all had at least 14.5 total hours of exposure to the
17 index case. Total time exposed to the index case during this period was the variable most
18 strongly associated with the probability of having a Mantoux test positive result (p<0.001) for
19 all variables and interactions considered. (**2++**)

Seating proximity of infected contacts to the index case

One study (N=760){337} found a statistically significant relationship between Mantoux test - positive contacts with no prior risk factors for tuberculosis, and seating proximity to an index patient with MDR TB on an aircraft (RR 8.5, 95%CI 1.7 to 41.3, p=0.01). (**3+**)

Three studies (N=120,{338} N=100,{339} and N=225){336} found no evidence that Mantoux test -positive contacts without prior risk factors for tuberculosis were more likely to be seated in closer proximity to an index case with tuberculosis on an aircraft than Mantoux test - positive contacts with prior risk factors. (**3+**)

11.3.4 From evidence to recommendations

The evidence base for this topic is prone to publication bias, where reports of successful tracing are more likely to be of interest, and therefore the yield of these procedures is likely to be overestimated.

One of the studies{334} had a crew member as an index case and assessed transmission to other crew. This is therefore a workplace study and not directly applicable to passenger-to-passenger transmission.

The evidence base indicates low yield from aircraft-based contact tracing, but proximity to the index case was seen to be a risk factor. However, identifying proximity is costly and difficult. Seating records, or even passenger lists, are not always available, and the onus of contacting passengers lies with the airline. Similar possibilities for transmission arise in other forms of long-haul transport, but seating plans are not generally available in these situations.

'Inform and advise' information is of limited utility in such situations, where risk of infection is extremely low, neither the TB service nor the airline know which passengers are more susceptible to infection, and the passengers receiving such information will not be in contact with a TB service from whom they can seek further advice face to face.

It was therefore felt that it was not an effective use of resources to conduct contact tracing among aircraft passengers or similar transport scenarios, unless a seating plan was available, or where exceptional circumstances exist.

Such exceptional circumstances were identified as including: an index case with MDR TB, frequent coughing, and a flight of over eight hours' duration. The eight hours threshold was recognised as fairly arbitrary, but is drawn from what little evidence exists. It is impossible to define 'frequent coughing' given a subjective assessment which may take place weeks after the flight. Clinical judgement will have to be used in any such case to identify how many passengers to advise the airline to send information to.

Where the index case is a crew member, contact tracing of individual passengers is not necessary as passengers will have had minimal exposure.

11.3.5 Recommendations

268. After diagnosis of TB in an aircraft traveller, do not routinely carry out contact tracing of fellow passengers. [2006, amended 2015]

269. The notifying clinician should inform the relevant consultant in communicable disease control or health protection if:

- less than 3 months has elapsed since the flight and the flight was longer than 8 hours, and
- the index case is sputum-smear-positive, and either
- the index case has multidrug-resistant TB, or

- the index case coughed frequently during the flight. **[2006]**

270. The consultant in communicable disease control or health protection should provide the airline with 'inform and advise' information to send to passengers seated in the same part of the aircraft as the index case. [2006]

271. If the TB index case is an aircraft crew member, contact tracing of passengers should not routinely take place. [2006]

272. If the TB index case is an aircraft crew member, contact tracing of other members of staff is appropriate, in accordance with the usual principles for screening workplace colleagues. [2006]

11.41 Contact tracing: cases in schools

11.4.12 Clinical introduction

TB in school pupils or staff requires particular attention because of the potential for spread of infection and also because of the anxiety that may arise among pupils, parents, staff and others. They should all be subject to individual risk assessment following discussion with the consultant in communicable disease control.

If the index case of TB is an adult member of staff, the purpose is to detect secondary cases elsewhere in the school, while if it is a pupil, the purpose is not only to detect secondary cases but also to find the source case, if it is not already thought to be known.

11.4.220 Methodological introduction

Studies were included that attempted to establish whether contact tracing was effective in identifying latent and active tuberculosis in school contacts exposed to an index case of tuberculosis in the school setting.

Six cohort studies and four non-analytic studies were found. None of the cohort studies were conducted in the UK, and only one non-analytic study took place in the UK. One cohort study{11} and one non-analytic study{340} were excluded due to methodological limitations, which are presented in Appendix K. Despite limited reporting of participant baseline characteristics, five cohort studies{341–345} and three non-analytic studies{346–348} were included.

11.4.320 Evidence statements

Case yields of latent tuberculous infection

Six studies{341–343},{345},{347},{348} investigated case yields of latent TB infection in school pupils with differing levels of exposure to an index case of sputum smear-positive TB. Latent TB infection yield was reported for the following four exposure categories:

- schools with index cases of TB disease in comparison to control schools with no reported index cases
- school pupils exposed to index cases of TB disease in comparison to pupils with no exposure to index cases
- school pupils with different levels of classroom contact to index cases of TB disease
- school pupils with direct classroom contact to index cases of TB disease in comparison to pupils with no classroom exposure to index cases.

The evidence for latent TB infection is presented in Table 42.

Table 42: Detection of latent TB in schools contact tracing

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils Mantoux test+	Association/statistical significance	Study location	Ref and NICE grade
1. Schools with pupil index cases*vs.*control schools	Four secondary schools *vs.* 10 secondary	277/3188 (8.7) *vs.* 123/3321 (3.7) [rrss]	$p<10^{-7}$	Italy	{343} 2+

rr Tine Test positive

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils Mantoux test+	Association/statistical significance	Study location	Ref and NICE grade
	schools				
	Two primary schools *vs.* three primary schools	51/722 (7.1) *vs.* 19/702 (2.7) [tt]	NS	Canada	{344} 2+
2. Exposed*vs.*non - exposed school pupils (pupil index cases)	All current high school pupils *vs.* non-exposed new school entrants	120/333 (36) *vs.* 39/248 (16)	RR 2.3 (95%CI 1.7 to 3.2, p<0.05)	USA	{342} 2+
	All high school graduates *vs.* non-exposed new school entrants	35/138 (25) *vs.* 39/248 (16)	RR 1.6 (95%CI 1.1 to 2.4, p<0.05)	USA	{342} 2+
	US-born current high school pupils *vs.* US-born new school entrants	27/145 (19) *vs.* 4/132 (3)	RR 6.1 (95%CI 2.2 to 17.9, p<0.05)	USA	{342} 2+
	US-born high school graduates *vs.* non-exposed US-born new school entrants	6/66 (9) *vs.* 4/132 (3)	RR 3.0 (95%CI 0.9 to 10.3)	USA	{342} 2+
3. Different levels of classroom exposure to pupil index cases	Junior high school pupils sharing one plus class *vs.* pupils entering a class recently vacated by index case	95/118 (81) *vs.* 30/88 (34)	Not reported	USA	{345} 2+
	Junior high school pupils sharing three *vs.* two *vs.* one class with index case	9/9 (100) *vs.* 32/35 (91) *vs.* 55/74 (74)	Not reported	USA	{345} 2+
	High school pupils sharing	7/13 (54) *vs.*	RR 5.7 (95%CI	USA	{341} 2+
	three plus *vs.* one plus (normally ventilated) *vs.* one plus	21/66 (32) *vs.* 25/106 (24)	3.26 to 10.13) *vs.* RR 4.2 (95%CI 2.6 to 6.75) *vs.* RR 3.2 (95%CI 2.0 to		

ss BCG vaccination was discontinued in Italy before the present research cohort were born, so tine test positivity could not be attributed to the booster effect

tt Prior BCG vaccination and foreign-born status were both significantly associated with Mantoux test positive outcome in all schools.

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils Mantoux test+	Association/statistical significance	Study location	Ref and NICE grade
	(normal or enhanced ventilation) classrooms with index case		5.18)		
4a. Pupils with*vs.*pupils without classroom exposure to pupil index cases	High school pupils sharing a classroom *vs.* pupils without classroom exposure	22/110 (20) *vs.* 54/616 (9)	RR 2.3 (95%CI 1.4 to 3.8)	USA	{342} 2+
	Secondary school pupils sharing a classroom *vs.* pupils without classroom exposure	76% tine test positive, nearly 11 times higher than pupils without classroom exposure	RR 10.9 (95%CI 8.7 to 13.4)	Italy	{343} 2+
	Primary school pupils sharing classrooms *vs.* pupils without classroom exposure	No significant difference in Mantoux test positive rates reported	Not reported	Canada	{344} 2+
4b. Pupils with*vs.*pupils without classroom exposure to teacher index cases	Primary school pupils sharing a classroom *vs.* pupils without classroom exposure	12/28 (43) *vs.* 3/27 (11)	Not reported	Ireland	{342},{343},{347}, {348} 3+

Case yields of active tuberculous disease

Three studies{343},{344},{347},{348} investigated case yields of active TB disease in school pupils with differing levels of exposure to an index case of sputum smear-positive TB. Active disease in contacts was variably defined as

- abnormal chest X-ray{342},{343},{347},{348}
- not specified by test result or site of disease{344}
- presence/absence of positive AFB sputum smear or X-ray findings compatible with cavitary disease.{343}

Active TB disease case yield was reported for the following two exposure categories:

- schools with index cases of TB disease in comparison to control schools with no reported index cases
- school pupils exposed to index cases of TB disease in comparison to pupils with no exposure to index cases.

The evidence for active TB disease is presented in Table 43.

Table 43: Summary of evidence: detection of active TB in schools contact tracing

Exposure category	Context of pupil exposure to TB index cases	Results N (%) pupils with TB disease	Statistical significance	Study location	Ref and NICE grade
Schools with index cases*vs.*control schools	Four secondary schools *vs.* 10 secondary schools	14/3188 (0.4) *vs.* 1/3321 (0.03)	Not reported	Italy	{343} 2+
	Two primary schools *vs.* three primary schools	1/722 (0.1) *vs*. 0/702	Not reported	Canada	{344} 2+
Pupils with*vs.*pupils without classroom exposure to teacher index cases	Primary school pupils sharing a classroom *vs.* pupils without classroom exposure	8/28 (29) *vs.* 0/27	Not reported	Ireland	{342},{343},{347}, {348} 3+

Case yields for a general TB outcome

One study conducted in the UK{342},{343},{347},{348} reported a general TB outcome (combined latent TB infection and active TB disease yield) for primary schools pupils with *vs.* those without classroom exposure to a teacher with sputum smear- and culture-positive tuberculous disease who developed symptoms over a three-month period prior to the outbreak.

31/46 (67%) pupils from two classrooms shared with the index case *vs.* 15/46 (33%) pupils from five non-exposed classrooms were diagnosed with TB infection or disease. No statistical significance testing was reported. (**3+**)

Transmission of tuberculosis disease from an index case to exposed school contacts verified by DNA fingerprint analysis

A study conducted in New Zealand{346} found that cases of active tuberculosis identified by contact tracing in secondary school pupils were confirmed by DNA fingerprint analysis to be due to direct transmission from school index cases. (**3+**)

- From evidence to recommendations

There are the following potential difficulties in making recommendations from the evidence base.

- There is a possibility of publication bias in the evidence base, where reports of successful tracing are more likely to be of interest, and therefore the yield of these procedures is likely to be overestimated.
- The evidence base does not take into account the country of birth or ethnicity of pupils, which is likely to be a confounding factor. In schools with a large proportion of pupils drawn from populations with high rates of TB, latent infection and active disease in some of those screened might erroneously be concluded as being due to transmission from the index case.
- Many of the studies conducted outside the UK were carried out in non-BCG vaccinated populations.

- Rates of disease are calculated on small denominators and are therefore imprecise.

The aim of contact tracing is different across age groups. In younger children a source is being sought, while in adolescents and adult staff members contact tracing is usually (but not invariably) the sole reason for the exercise.

The GDG were keen to limit the resources that might be consumed by these large and mainly unproductive exercises, and agreed that initially, only children in the same class as the index case need to be assessed. School registers may help in identifying the pupils at highest risk.

After-school, sports and religious activities should also be kept in mind where the degree of contact might be equivalent to classroom contact. The GDG agreed that outdoor activities would not normally pose a risk of TB transmission, unless this involved confined spaces for prolonged time periods, for example camping. Such obvious exceptions were not felt to require a recommendation.

11.4.44 Recommendations

273. After diagnosis of TB in a school pupil or member of staff, the consultant in communicable disease control or health protection should be prepared to explain the prevention and control procedures to staff, parents and the press. Advice on managing these incidents and their public relations is available from the Public Health England Health Protection Team and the local authority. [2006, amended 2015]

274. If a school pupil is diagnosed with sputum-smear-positive TB, carry out a risk assessment of the need to test the rest of his or her class (if there is a single class group), or the rest of the year group who share classes, as part of contact tracing. [2006]

275. If a teacher has sputum-smear-positive TB, assess the pupils in his or her classes during the preceding 3 months as part of contact tracing. [2006]

276. Consider extending contact tracing in schools to include children and teachers involved in extracurricular activities, and non-teaching staff, on the basis of:

- the degree of infectivity of the index case
- the length of time the index case was in contact with others
- whether contacts are unusually susceptible to infection
- the proximity of contact. **[2006, amended 2015]**

277. Treat secondary cases of sputum-smear-positive TB as index cases for contact tracing. [2006]

278. If the index case of a school pupil's TB infection is not found, and the child is not in a high-risk group for TB, contact tracing and screening (by either symptom enquiry or chest X-ray) should be considered for all relevant members of staff at the school [2006]

11.5 Contact tracing: community childcare

11.5.1 Clinical introduction

Children, particularly of pre-school age, are more likely to acquire TB infection, and progress to TB disease, than older children and adults if they are exposed to infectious tuberculosis – usually from adults. Each year in England and Wales there are a number of incidents where children in nurseries and other childcare facilities are screened for tuberculosis after exposure to an adult staff member. Government policy and social changes mean that more children will be found in childcare settings. An increasing number of adults will therefore be in contact with children up to age 16 years.

11.5.2 Methodological introduction

Studies investigating whether there were specific management strategies that were effective in preventing and controlling the transmission of TB infection and disease in childcare settings were sought. One cohort study was found that addressed the question.

The study, conducted in a hospital nursery setting in the USA{349} focused on screening for tuberculosis in infants and healthcare workers exposed to an index case of TB disease. Selection of infants to different TB screening procedures was based on level of TB exposure. Mantoux test conversion rates in healthcare workers who worked in the nursery unit when the index case was present were compared with healthcare workers in the hospital who had not worked in the unit.

11.5.3 Evidence statements

Latent TB infection in infants and healthcare workers with high versus low risk of exposure to an index case of TB

No difference between high and low exposure groups in the number of tuberculin-positive reactions was identified.{349} The evidence is summarised in Table 44

Table 44: Summary of evidence: detection of latent TB in community childcare

Patient group and exposure status	N (%) Mantoux test positive reactors in participants with low exposure to the index case	N (%) Mantoux test positive reactors in participants with high exposure to the index case	Statistical significance	NICE grade
Infants				
Low/high exposure shared unit with index case 8–12/0–8 weeks prior to diagnosis	1/259 (7 mm reaction at age 11 weeks, received BCG vaccination at age three days)	0/139 (including 30 aged more than 56 days)	Not reported	2+
Healthcare workers				
Low/high exposure never worked in unit/worked in unit during index case stay	14/619 (2.26) converted	4/130 (3.08) converted	NS p<0.6	2+

Completion rate for isoniazid prophylaxis among high-exposure infants

132/139 (95%) infants with high exposure to an index case of TB disease completed a three month course of isoniazid prophylaxis.{349} (**2+**)

11.5.41 From evidence to recommendations

2 There is no relevant evidence on which to base recommendations. Because of the lack of an
3 infrastructure to provide screening for this very diverse setting, which includes informal care
4 arrangements, recommendations deal only with contact tracing.

11.5.55 Recommendations

6 **279. When an adult who works in childcare (including people who provide childcare**
7 **informally) is diagnosed with sputum-smear-positive TB, manage as for contact**
8 **tracing. [2006]**

9

11.6 Contact tracing: cases in hospital inpatients

11.6.1 Clinical introduction

With the increasing numbers of clinical cases of tuberculosis, some of whom are admitted to hospital, there are incidents where patients with tuberculosis are not appropriately isolated, leading to potential exposure of other patients, some of whom may have reduced immunity. Such incidents are not strictly outbreaks, but may consume considerable resources identifying exposed patients, many of whom are at minimal risk.

A further type of incident is where a healthcare worker is found to have active tuberculosis, with patients being exposed to possible infection risks. This latter type of incident often involves staff recruited from overseas, who may only have been screened to healthcare worker level and not to the higher level advised for new entrants from high-incidence settings (see section 12.1).

Finally, there have been true outbreaks where patients, usually but not exclusively HIV co-infected, have acquired active tuberculosis disease from other inpatients, often due to failure to use appropriate infection control measures, or because facilities thought to be negative pressure were not actually so.{232} Such outbreaks, particularly when of MDR TB transmission, can have a high mortality and morbidity, as well as major medicolegal implications for NHS trusts.{232}

11.6.2 Methodological introduction

Studies that investigated whether contact tracing was effective in identifying latent tuberculosis infection and active tuberculosis disease in patient and staff contacts exposed to an index case of tuberculosis in the hospital setting were targeted.

One case control study and four non-analytic studies were identified. The case control study from the USA{350} evaluated a contact tracing investigation of hospital staff conducted in relation to an index patient diagnosed with tuberculosis disease from an extrapulmonary site. Despite limited reporting of baseline characteristics, and no significance testing for the outcome of Mantoux test converters in exposed cases and non-exposed controls, the study was included. Two non-analytic studies from the UK{351} and the USA{352} were included.

Three non-analytic studies from the USA{353} and the UK{232},{354} were excluded due to methodological limitations, which are presented in Appendix K.

11.6.3 Evidence statements

Case yields of latent tuberculous infection

Two studies{350},{352} investigated latent TB infection in staff with different levels of exposure to index cases of active TB disease in hospital settings. Neither of the studies was conducted in the UK.

The evidence for latent TB infection is presented in Table 45.

Table 45: Detection of latent TB in contact tracing among health care workers (HCWs)

Exposure category	Exposure content	Results Healthcare workers with Mantoux test conversions, N (%)	Association/statistical significance	Ref and NICE grade
Exposed*vs.*non-exposed healthcare workers	Nurses exposed to index case after surgery *vs.*	12/95 (13) *vs.* 2/1435 (0.14) *vs.* 0/23	Not reported	{350} 2+

Exposure category	Exposure content	Results Healthcare workers with Mantoux test conversions, N (%)	Association/statistical significance	Ref and NICE grade
(non- pulmonary patient index case)	nurses and students exposed prior to surgery *vs.* non-exposed historical control nurses			
Exposed*vs.*non-exposed healthcare workers (healthcare workers index case)	Healthcare workers on two wards (A and B) *vs.* healthcare workers on non-exposed wards	Ward A 21/70 (30) *vs*. 10/76 (13.2) non-exposed wards	RR 2.3 (95%CI 1.2 to 4.5, p=0.02)	{352} 3+
		Ward B 29/61 (47.5) *vs.* 10/76 (13.2) non-exposed wards	RR 3.6 (95%CI 1.9 to 6.8, p<0.001)	{352} 3+
		Controlling for exposure to infectious TB patients (N=25): risk of Mantoux test conversion remained higher for healthcare workers on wards A and B	Weighted RR 3.0 (95%CI 1.9 to 4.5, p<0.001)	{352} 3+

Case yields of active tuberculous disease

Two studies{351},{352} investigated case yields of active TB disease in patients and staff in hospitals where index cases of active TB disease had been identified. One of the studies was conducted in the UK. Active TB disease case yields were reported for the following:

- staff with and without exposure to TB index cases
- hospital staff, surgical patients and renal patients exposed to a TB index case.

The evidence for active TB disease is presented in Table 46 below.

Table 46: Detection of active TB in contact tracing among healthcare workers

Population	Exposure to healthcare workers index cases	Results Healthcare workers with TB disease, N (%)	Statistical significance	Ref and NICE grade
Exposed*vs.*non-exposed healthcare workers	HCWs exposed on two wards (A and B) *vs.* Healthcare workers on non-exposed wards	8/51 (16) wards A and B *vs*. 0/76 non-exposed wards	Not reported	{352} 3+
Healthcare workers*vs.*renal patients*vs.*surgical patients	All groups exposed in a hospital	0/135 *vs.* 1/220 (0.45%) *vs.* 0/57	Not reported	{351} 3+

Type of exposure to the index case

One study{350} found that exposure to the surgical wounds of an index case of non-pulmonary TB was significantly associated with latent TB among previously Mantoux test - negative nurses.

Irrigation or packing of the wound was the only statistically significant risk factor for a positive Mantoux test (OR 9, 95%CI 1.2 to 67, p=0.03), with nurses involved in these activities having nine times the risk of Mantoux test conversion compared to nurses not involved in substantial wound care. (**2+**)

Duration of exposure

Hospital staff Mantoux test converters and index cases worked more total shifts on two wards with infectious TB cases than staff who were Mantoux test negative (Ward A median 80 *vs*. four shifts, p=0.004; Ward B median 124 *vs.* five shifts, p<0.001).{352} (**3+**)

11.6.4 From evidence to recommendations

The wide variety of settings and possibilities mean that narrowly drawn guidelines are not appropriate. The pick-up from contact tracing exercises is very low so it is important to avoid unnecessary screening. Evidence from North America may show levels of potential transmission, but is not particularly relevant for the effectiveness of service models in the UK. The GDG's considerations were otherwise constrained by the paucity of evidence relevant to the UK.

Awareness of tuberculosis and transmission risks needs to be maintained in healthcare workers who work with immunocompromised patients – for example surgeons who work with transplant patients, and oncologists. A rigorous risk assessment was regarded as useful before any action is taken.

The GDG recognised the need to limit contact tracing exercises to instances where there is a genuine risk of TB transmission, and chose eight hours as a time threshold for exposure. There is no evidence to support this, but it is in line with the threshold given elsewhere for contact tracing.

11.6.5 Recommendations

280. If TB is diagnosed in a hospital inpatient, do a risk assessment. This should take into account:

- the degree of infectivity of the index case
- the length of time before the infectious patient was isolated
- whether other patients are unusually susceptible to infection
- the proximity of contact. **[2006, amended 2015]**

281. Carry out contact tracing and testing only for patients for whom the risk is regarded as significant. [2006]

282. Regard patients as at risk of infection if they spent more than 8 hours in the same bay as an inpatient with sputum-smear-positive TB who had a cough. Document the risk in the contact's clinical notes, for the attention of the contact's consultant. Give the contact 'inform and advise' information, and inform their GP. [2006]

283. **If patients were exposed to a patient with sputum-smear-positive TB for long enough to be equivalent to household contacts (as determined by the risk assessment), or an exposed patient is known to be particularly susceptible to infection, manage their TB risk in the same way as household contacts. [2006, amended 2015]**

284. **If an inpatient with sputum-smear-positive TB is found to have multidrug-resistant TB, or if exposed patients are HIV positive, trace contacts following the Interdepartmental Working Group on Tuberculosis guidelines. [2006]**

285. **In cases of doubt when planning contact tracing after diagnosing sputum-smear-positive TB in an inpatient, seek further advice from the local or national Public Health England or Wales unit or people experienced in the field. [2006, amended 2015]**

11.7 Street homeless people

11.7.1 Clinical introduction

Deprivation has long been associated with tuberculosis. Much higher rates of tuberculosis disease in street homeless people and hostel dwellers have been recognised for many years{362},{363}. Chest X-ray screening of homeless people attending a soup kitchen in London in 1993{364} showed 4.3% with X-ray changes suspicious of active tuberculosis of which 1.5% (1,500/100,000) were confirmed as having bacteriologically confirmed active disease. The great majority of such street homeless people in the UK up to the late 1990s were men of white ethnicity, whose rate of tuberculosis from national data would normally be expected to be in the range of 5/100,000 per annum.{26},{140}

11.7.2 Methodological introduction

Studies that compared different methods of screening for latent tuberculosis infection and active tuberculosis disease in homeless people in order to evaluate which method was most effective were targeted.

Six non-analytic studies focused on different tuberculosis screening methods applied to homeless participants. None of the studies reported the results of interferon-gamma immunological testing in homeless people. Four studies{308},{328},{365},{366} did not make comparisons between the different screening methods they reported and were excluded.

Two studies{367},{368} conducted in the UK and the USA compared homeless people diagnosed with active tuberculosis with their prior test results on symptom questionnaire, tuberculin skin test, and chest X-ray. The studies were included despite having the following methodological limitations.

- The number of people approached for screening and resultant screening uptake was not clearly reported.
- Not all tests were read and no explanation for this was provided.
- Some studies offered incentives to attend for screening, while others did not.
- Those involved in collecting prospective data via interviews were aware of retrospective findings that categorised subjects by clinical outcome.
- It was not reported how screening tests were conducted and read and by whom.
- Screening methods used did not show a combination of good sensitivity and specificity.
- Uptake of screening varied between 40–90% at different sites.
- Investigators did not state whether tests were performed blindly or independently.
- Statistical significance testing was not done.

11.7.3 Evidence statements

Comparative effectiveness of symptom questionnaire, tuberculin skin test and chest X-ray for detecting latent tuberculous infection

One retrospective study{367} found that tuberculin skin testing was more effective in detecting latent tuberculosis and eligibility for treatment for latent TB infection in homeless people than either symptom questionnaire or chest X-ray. The evidence is presented in Table 47.

Table 47: Summary of evidence: detection methods for latent TB

People with abnormal symptom questionnaire scores	People with positive tuberculin skin test results, Heaf grade 4	People with abnormal chest X-ray results	Statistical significance	NICE grade
0/5 with Heaf grade 4 (0% sensitivity)	5/5 prescribed treatment for latent TB infection (100% sensitivity)	0/5 with Heaf grade 4 (0% sensitivity)	Not reported	3+

Comparative effectiveness of symptom questionnaire, tuberculin skin test and chest X-ray for detecting active tuberculous disease

Two retrospective studies,{367},{368} did not find consistent evidence that any of the three screening methods compared were more effective than the others in detecting signs and symptoms of TB in homeless people subsequently diagnosed with active tuberculosis. Evidence is summarised in Table 48 below.

Table 48: Summary of evidence: detection methods for active TB

N (%) TB disease cases with abnormal symptom questionnaire scores	N (%) TB disease cases with tuberculin skin test positive scores	N (%) TB disease cases with abnormal chest X-ray results	Statistical significance	Ref and NICE grade
2/10 (20) reported haemoptysis	1/10 (10) (7/10 cases did not have Mantoux test)	8/10 (80)	Not reported	{367},{368} 3+
13/16 (81), sensitivity 81%, specificity 51%, PPV 23%, NPV 94%	11/16 (69), sensitivity 69%, specificity 83%, PPV 42%, NPV 94%	5/16 (31), sensitivity 31%, specificity 94%, PPV 50%, NPV 88%	Not reported	{367};{368} 3+
PPV = Positive predictive value; NPV = Negative predictive value.				

11.7.4 From evidence to recommendations

The rate of TB in street homeless people is still high. This group is difficult to reach. Emphasis should therefore be on active case finding, which may have to be done on an opportunist and/or symptomatic basis. In urban settings, digital chest X-ray provides fast results for likely active disease.

Simple incentives for attending screening, such as hot drinks or snacks, may be useful. Because of the mobility of this group, tuberculin skin testing and interferon-gamma testing were felt to be less useful generally, because people may move before test reading and are also not likely to complete treatment for latent TB infection. The important role of the TB service was recognised in promoting awareness of TB, and who to contact, among those working with homeless people, including primary care professionals, and the social and voluntary sectors.

The GDG were unable to make a service configuration recommendation on the frequency of screening in this group, given the lack of any evidence to guide them.

11.7.5 Recommendations

286. In areas of identified need (see section 1.8.6), including major urban centres with a high incidence of TB, commissioners should:

- ensure there is a programme of active case-finding using mobile X-ray in places where homeless people and people who misuse substances congregate (this includes: homeless day centres, rolling shelters, hostels and temporary shelters established as part of cold weather initiatives and venues housing needle and syringe programmes)
- base the frequency of screening at any one location on population turnover
- where local demand does not warrant a mobile X-ray team, consider commissioning mobile X-ray capacity from another area. **[2006, amended 2012]**

287. Multidisciplinary TB teams should consider using simple incentives, such as providing hot drinks and snacks, to encourage people to attend for screening. [2006, amended 2012, amended 2015]

288. Commissioners of TB prevention and control programmes should consider offering people who are homeless and people who misuse substances other health interventions when they are screened for TB at a mobile X-ray unit. (Examples may include blood-borne virus screening, dentistry and podiatry services.) [2012]

289. Multidisciplinary TB teams should work closely with mobile X-ray teams and frontline staff in hostels and day centres to promote TB screening and to ensure appropriate onward referrals and follow-up. [2012]

290. Multidisciplinary TB teams should consider using peer educators to promote the uptake of TB screening in hostels and day centres. [2012]

291. Multidisciplinary TB teams should provide routine data to TB control boards on: screening uptake, referrals and the number of active TB cases identified. [2012]

12 Preventing infection in specific settings

12.1 Healthcare environments: new employees

12.1.1 Clinical introduction

Studies in the late 1980s suggested that the incidence of TB in healthcare workers, with the general exception of mortuary workers, was no higher than that of the general population.{369} More recently however a study found a twofold increased risk among healthcare workers.{300} Also more recently the NHS has been recruiting staff, particularly nurses, from developing countries with a high incidence of tuberculosis. This is acknowledged as an essential area for improvement in the 2004 Chief Medical Officer's TB Action Plan{2} which gives as a goal: 'achieve comprehensive occupational screening of healthcare workers joining the NHS'.

12.1.2 Methodological introduction

Studies on the prevention of TB transmission in newly employed staff in hospital settings were sought. Only one non-analytic study{370} met the inclusion criteria.

Studies focusing on pre-employment screening measures to prevent and control the transmission of TB in healthcare workers with HIV infection were also targeted. No evidence was found, and hence there are no evidence statements for this area.

12.1.3 Evidence statements

TB prevention and control measures in pre-employment occupational health screening

One retrospective non-analytic study{370} reported on the following interventions for pre-employment occupational health screening in West Midlands NHS hospitals:

- identification of new doctors eligible for TB screening
- identification of new doctors and nurses at risk for active tuberculous disease
- appropriateness of tuberculin skin testing for new employees.

Evidence is summarised in Table 49.

Table 49: Summary of evidence: pre-employment screening

Intervention	Occupational health service pre-employment screening	NICE grade
Doctors eligible for TB screening, N (%)	Identified 7/14 (50) new doctors who developed active TB disease during employment.	3+
Healthcare workers at risk for active TB disease, measured by Heaf test grade	• Did not act on evidence of TB transmission in newly appointed doctors, and found no evidence of TB transmission in newly- appointed nurses. • 3/7 new doctors Mantoux test positive (grades 3–4) subsequently diagnosed with active TB via self-referral with symptoms. • Six new nurses Mantoux test negative (grades range 0–2) subsequently diagnosed with active TB.	3+
Mantoux test, Heaf test	• Inappropriately applied Mantoux tests to 13/26 new employees. • Two without prior BCG vaccination were not tested	3+

Intervention	Occupational health service pre-employment screening	NICE grade
	and developed TB disease. • Nine with prior BCG vaccination were tested. • 1/2 with unknown BCG status was tested.	

12.1.4 From evidence to recommendations

This guideline is not intended to duplicate the guidance which was, at the time of writing, being drafted by the Department of Health ('Health clearance for serious communicable diseases: new health care workers').

The recommendations are also guided by the advice of the Chief Medical Officer to the NHS in England to 'achieve comprehensive occupational screening of healthcare workers joining the NHS'.{2}

There is a possibility that new employees in healthcare environments who have recently entered the UK can miss out on the advanced level of screening given to new entrants. In this regard, the recommendations refer the reader to the section of the guideline for new entrants.

Limitations in pre-employment screening techniques are reported in the evidence base. Consequently, the GDG agreed that symptoms should be screened first, possibly by questionnaire, as a way to identify any new staff who may have active tuberculosis. Chest X-rays are the first choice of test for those with signs or symptoms.

For the majority of new employees without any signs or symptoms, resources should be used effectively by carrying out an individual risk assessment and choosing screening techniques accordingly. This is familiar current practice for many occupational medicine departments.

The recommendations aim to make sure that new employees are screened before commencing work. It was noted that the NICE guideline cannot dictate screening techniques to non-NHS agencies, and also that such screening may be carried out in other countries with attendant difficulty in receiving documentation. However, the health risks associated with employing an infectious member of staff were deemed to warrant a thorough check before they start work.

The evidence base does not support a significant departure from the details of the recommendations in the BTS code of practice.{6}

Although the evidence is limited to hospitals, the recommendations are applicable to primary as well as secondary care, and to ancillary as well as clinical staff.

12.1.5 Recommendations

292. Employees new to the NHS who will be working with patients or clinical specimens should not start work until they have completed a TB screen or health check, or documentary evidence is provided of such screening having taken place within the preceding 12 months. [2006]

293. Employees new to the NHS who will not have contact with patients or clinical specimens should not start work if they have signs or symptoms of TB. [2006]

294. Health checks for employees new to the NHS who will have contact with patients or clinical materials should include:

- assessment of personal or family history of TB
- asking about symptoms and signs, possibly by questionnaire
- documentary evidence of TB skin (or interferon-gamma release assay) testing and/or BCG scar check by an occupational health professional, not relying on the applicant's personal assessment
- Mantoux result within the past 5 years, if available. **[2006]**

295. See recommendations 19 to 22 for screening new NHS employees for latent TB. [2006]

296. Employees who will be working with patients or clinical specimens and who are Mantoux negative[uu] should have an individual risk assessment for HIV infection before BCG vaccination is given. [2006, amended 2015]

297. Employees of any age who are new to the NHS and are from countries of high TB incidence, or who have had contact with patients in settings with a high TB prevalence should have an interferon-gamma release assay. If negative, offer BCG vaccination as with a negative Mantoux result[vv]. If positive, refer the person for clinical assessment for diagnosis and possible treatment of latent infection or active disease. [2006, amended 2011]

298. If a new employee from the UK or other low-incidence setting, who has not had a BCG vaccination, has a positive Mantoux test[ww] (see section 1.2.1) and a positive interferon-gamma release assay, they should have a medical assessment and a posterior-anterior chest X-ray. They should be referred to a TB clinic to determine whether they need TB treatment if the chest X-ray is abnormal, or to determine whether they need treatment of latent TB infection if the chest X-ray is normal. [2006, amended 2011, amended 2015]

299. If a prospective or current healthcare worker who is Mantoux negative[xx] declines BCG vaccination, explain the risks and supplement the oral explanation

[uu] Although not updated by a new review, the Committee felt strongly that the threshold for test positivity in healthcare workers should be brought in line with both international guidance and the other recommendations in this section. The threshold for test positivity of 6 mm from the 2011 NICE guideline is inconsistent with the new recommendations, which opted for a threshold of 5 mm, as well as with the new clinical- and cost-effectiveness reviews and the new health economic modelling on which these were based. This is particularly an issue given that the 2011 recommendations were consensus-based, not driven by evidence. For this reason, the recommendation now simply references the recommendations on the diagnosis of latent TB infection. See section 4.1.3.4 for further information.

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[xx] Although not updated by a new review, the Committee felt strongly that the threshold for test positivity in healthcare workers should be brought in line with both international guidance and the other recommendations in this section. The threshold for test positivity of 6 mm from the 2011 NICE guideline is inconsistent with the new

with written advice. If the person still declines BCG vaccination, he or she should not work where there is a risk of exposure to TB. The employer will need to consider each case individually, taking account of employment and health and safety obligations. [2006]

300. Screen clinical students, agency and locum staff and contract ancillary workers who have contact with patients or clinical materials for TB to the same standard as new employees in healthcare environments, according to the recommendations set out above. Seek documentary evidence of screening to this standard from locum agencies and contractors who carry out their own screening. [2006]

301. NHS trusts arranging care for NHS patients in non-NHS settings should ensure that healthcare workers who have contact with patients or clinical materials in these settings have been screened for TB to the same standard as new employees in NHS settings. [2006]

recommendations, which opted for a threshold of 5 mm, as well as with the new clinical- and cost-effectiveness reviews and the new health economic modelling on which these were based. This is particularly an issue given that the 2011 recommendations were consensus-based, not driven by evidence. For this reason, the recommendation now simply references the recommendations on the diagnosis of latent TB infection. See section 4.1.3.4 for further information.

12.21 Healthcare environments: occupational health

12.2.12 Clinical introduction

3 TB is transmitted through the aerosol route. Hitherto, best practice in hospitals{6} has been
4 that patients with suspected pulmonary tuberculosis are initially admitted to single rooms,
5 vented to the outside, until their sputum status is known and risk assessments for
6 infectiousness and MDR TB are made. The risk assessment should also take into account
7 the immune status of other patients on the ward. These measures should greatly reduce the
8 chance of transmission to staff, but surveys of infection control practice show poor
9 adherence.{371}

10 Readers should be aware of the Health and Safety Executive guidance in this area,
11 'Biological agents: managing the risks in laboratories and healthcare premises' (available
12 from www.hse.gov.uk).

12.2.213 Methodological introduction

14 Studies on the prevention of TB transmission in staff currently employed in hospital settings
15 were sought. One cohort study and four non-analytic studies were found.

16 Five non-analytic studies from the USA{233},{372–375} were excluded due to
17 methodological limitations, presented in Appendix K. One non-analytic study from the
18 UK{371} while methodologically sound, was excluded as it addressed the extent to which TB
19 infection control measures recommended by guidelines were applied in practice, but did not
20 seek to evaluate the effectiveness of recommended measures.

21 One cohort study{376} and four non-analytic studies{235},{370},{377},{378} reported
22 evidence on the following:

23 • effects of new infection control measures in reducing TB transmission in hospital workers
24 • the association between ventilation controls and tuberculin skin test conversion in hospital
25 workers
26 • effectiveness of occupational health screening for identifying cases of active tuberculous
27 disease in hospital workers
28 • effects of serial tuberculin skin tests in BCG vaccinated hospital workers.

29 Studies on screening measures to prevent and control the transmission of TB in employed
30 healthcare workers with HIV infection were also targeted. No evidence was found that met
31 the inclusion criteria, and hence there are no evidence statements for this area.

12.2.32 Evidence statements

33 Effects of new infection control measures in reducing tuberculosis transmission in 34 hospital workers

35 Evidence statements are presented in Table 50.

36 **Table 50: Summary of evidence: infection control measures**

New infection control measures	Population	N (%) decrease in healthcare worker Mantoux test conversion rate in response to new measures	Association/statistical significance	Ref and NICE grade
1) Introduction of new	Emergency	Baseline: 6/50	RR 5.9 (95% CI 2.7	{376}

New infection control measures	Population	N (%) decrease in healthcare worker Mantoux test conversion rate in response to new measures	Association/statistical significance	Ref and NICE grade
respiratory isolation rooms. 2) Ventilation with at least 25% fresh air in the work area.	department staff (intervention group) *vs.* other hospital workers not benefiting from interventions	(12) *vs.* 51/2514 (2)	to 13.1); absolute difference 10% (95% CI 1% to 19%).	2+
3) Laminar airflow from staff to patients. 4) Plastic droplet shields for staff.		Post-intervention: 0/64 *vs.* 36/3000 (1.2)	RR not calculable; absolute difference 1.2% (95% CI 1% to 2%)	{376} 2+
1) Higher diagnostic suspicion for infectious TB. 2) Stricter criteria for discontinuation of patient isolation. 3) Stricter criteria for patient adherence to isolation procedures and use of respiratory protection when outside isolation rooms. 4) Restriction of sputum induction and aerosolised pentamidine treatment to isolation rooms. 5) Expansion of anti-TB therapy to include at least two more drugs. 6) Improvements to negative pressure rooms. 7) Upgraded respiratory protection for employees. 8) Improvement in speed of return for diagnostic tests.	Susceptible healthcare workers on an HIV ward	Initial period 7/25 (28) to early follow-up 3/17 (18) to late follow-up period 0/23	p<0.01	{235} 3+

The association between ventilation controls and tuberculin skin test conversion in hospital workers

Evidence statements are presented in Table 51.

Table 51: Summary of evidence: ventilation

Association	Mantoux test conversion rates in healthcare workers	Association/statistical significance	Ref and NICE grade
Ventilation in non-isolation rooms and risk of latent TB infection	Shorter time to conversion significantly associated with being in a non-isolation room with less than two air exchanges *vs.* a room with two plus air exchanges per hour.	Hazard ratio: 3.4 (95% CI 2.1 to 5.8)	{377} 3+
Ventilation in respiratory isolation rooms and risk of latent TB infection	No significant difference in time to conversion for isolation rooms with less than six air exchanges	Hazard ratio: 1.02 (95% CI 0.8 to 1.3)	{377} 3+

Association	Mantoux test conversion rates in healthcare workers	Association/statistical significance	Ref and NICE grade
	vs. those with six plus air exchanges per hour.		
Inadequate ventilation and risk of latent TB infection in nurses and housekeeping staff	Rates significantly associated with inadequately ventilated non-isolation and isolation rooms.	p<0.001	{377} 3+
Inadequate ventilation and risk of latent TB infection in respiratory therapists	Rates significantly associated with inadequate ventilated non-isolation and bronchoscopy rooms.	p<0.001	{377} 3+

Effectiveness of occupational health screening for identifying cases of active tuberculous disease in hospital workers

One study{370} found that occupational health screening in West Midlands NHS hospitals detected fewer cases of active TB in employees than self-referral or contact tracing exercises.

Over a three-year period occupational health surveillance detected one (3.8%) case of active TB *vs.* 23 (88%) TB cases who self-referred with symptoms, and two cases (7.6%) detected via contact tracing exercises. Statistical significance testing was not done. (**3+**)

Effects of serial tuberculin skin tests in BCG vaccinated hospital workers

One prospective study{378} found that an initial Mantoux test, followed by a repeat Mantoux test administered one week later to BCG vaccinated hospital employees resulted in an increased diameter of induration for the repeat test relative to the first test when read at 48 hours. This was followed by a decreased induration for the repeat test relative to the first at 72 hours.

Mean induration diameter was 7.1 mm for test 1 *vs.* 14.9 mm for repeat test at 48 hours (mean change 7.8 mm; 95%CI 4.2 to 11.4 mm, p<0.001). There was no difference between the tests at 72 hours (mean induration diameter 9.5 mm at test 1 versus 9.7 mm on repeat test, mean change 0.2 mm; 95%CI −4.0 mm to 4.4 mm, p=0.93). (**3+**)

12.2.4 From evidence to recommendations

The evidence base is not easily applicable to a UK NHS setting. Studies to assess the impact of certain isolation and infection control procedures have been performed in North America, using tuberculin skin test conversion (not performed in this context in the UK) as a marker of infection. The population of staff on which these studies are performed is also generally not BCG vaccinated.

There is a duty on staff to report symptoms as part of protecting patients.{62},{379}

Annual reminders are appropriate as a regular intervention in selected staff members, and this is best done at the same time as other annual reminders, for example influenza vaccination. In staff in general, it was felt that the recommendations should promote awareness through 'inform and advise' information.

12.2.5 Recommendations

302. Include reminders of the symptoms of TB, and the need for prompt reporting of such symptoms, with annual reminders about occupational health for staff who:

- are in regular contact with TB patients or clinical materials, or
- have worked in a high-risk clinical setting for 4 weeks or longer.

Give one-off reminders after a TB incident on a ward. **[2006]**

303. If no documentary evidence of previous screening is available, screen staff in contact with patients or clinical material who are transferring jobs within the NHS as for new employees. [2006]

304. Assess the risk of TB for a new healthcare worker who knows he or she is HIV positive at the time of recruitment as part of the occupational health checks. [2006]

305. The employer, through the occupational health department, should be aware of the settings with increased risk of exposure to TB, and that these pose increased risks to HIV-positive healthcare workers. [2006]

306. Healthcare workers who are found to be HIV positive during employment should have medical and occupational assessments of TB risk, and may need to modify their work to reduce exposure. [2006]

12.3 Prisons and remand centres

12.3.1 Clinical introduction

In some countries the prison system acts as an amplification system for tuberculosis, with infected inmates causing transmission both within the prison and also in the community after discharge – either while still infectious or without adequate treatment and follow-up arrangements (or both). TB in the prison system of England and Wales was not thought to be a significant problem in the 1980s.{380} Prisoners however are likely to disproportionately include those with social and deprivation risk factors for TB (for example, social exclusion or drug abuse).

More recently, TB in prisons has increased and one community prison in London has been shown to be involved with the transmission of TB in an ongoing isoniazid-resistant TB outbreak.{329}

The 2005 Chief Medical Officer's TB Action Plan{2} sets improvements in prison care as one of the essential activities to be undertaken in improving TB care: 'achieve good coverage of prisons, with arrangements in particular for rapid assessment of suspected cases, supervision of prisoners' TB treatment, and maintenance of uninterrupted care by liaising with the services in their new area of residence prior to their release'. It also calls for strengthened surveillance of TB in prisons.

Throughout this section, the guideline uses the following terminology: in the USA, *jails* mostly house pre-trial detainees or inmates with short-duration sentences, whereas *prisons* house sentenced inmates for longer durations. In the UK, pre-trial detainees are housed in *remand centres* until completion of the trial and sentencing, while sentenced inmates are located in *prisons*. Remand and sentenced prisoners are often mixed within local prisons. In all these circumstances, those detained are referred to as *prisoners*.

12.3.2 Current practice

The review of current services shows that TB service providers either care for prisoners in clinics, or go on prison visits. Prior to the integration of prison medical services into the NHS, prisons would typically have arrangements for secondary care with one local hospital trust. Excluding those that stated that there was no prison or remand centre in their area, about a third cared for prisoners in clinics and a slightly higher proportion undertook prison visits, although some of these were not routine.

12.3.3 Methodological introduction

Studies investigating whether there were effective strategies for the prevention and control of the transmission of TB infection and disease in prisons were targeted. Two randomised controlled trials{206},{208} and four non-analytic studies{381–384} were found. However, two of these{383},{384} were excluded due to methodological limitations presented in Appendix K. The studies were all conducted in the USA in either prison or jail settings.

12.3.4 Evidence statements

Comparing strategies used in prisons to facilitate completion of prophylaxis in prisoners released back into the community

Two RCTs{206},{208} compared:

- one TB education session *vs.* one TB education session plus a financial incentive
- one TB education session *vs.* one TB education session plus a financial incentive *vs.* TB education sessions administered every two weeks for the duration of an inmate's stay.

The evidence is presented in Table 52.

Table 52: Summary of evidence: educational interventions in prisons

Outcomes	One TB education session control	TB education session plus financial incentive	TB education sessions administered every 2 weeks	Association/statistical significance	Ref and NICE grade
N (%) attendance at follow-up community clinic appointment	7/30 (23.3)	8/31 (25.8)	N/A	NS OR 1.43 (95% CI 0.35 to 3.71, p=0.82)	{206} 1+
	25/104 (24)	42/114 (37)	40/107 (37)	Adjusted OR (pooled results for education and incentive groups): 1.85 (95% CI 1.04 to 3.28, p=0.04)	{208} 1+
N (%) completed prophylaxis	2/31	2/30	N/A	Not reported	{206} 1+
	12/25 (48)	14/42 (33)	24/37 (65)	p=0.02	{208}1+
			Over twice as likely to complete than control group	Adjusted OR 2.2 (95% CI 1.04 to 4.72, p=0.04)	{208} 1+
		Completion		Adjusted OR 1.07	{208}

Outcomes	One TB education session control	TB education session plus financial incentive	TB education sessions administered every 2 weeks	Association/statistical significance	Ref and NICE grade
		no different from control group		(95% CI 0.47 to 2.4)	1+

Strategies used to facilitate prevention and control of TB infection and disease within prisons

One non-analytic study{381} investigated the use of screening strategies to detect TB disease in incarcerated inmates.

The evidence is summarised in Table 53.

Table 53: Summary of evidence: detection of active TB in prisons

Population	Prior history/TB symptom reports	Routine TB screening (Mantoux test and chest X-ray)	Cases detected by contact tracing	Statistical significance	NICE grade
N (%) new inmates	13/53 (24)	39/53 (74)	N/A	Not reported	3+
N (%) longer-term inmates (≥ six months)	31/43 (72)	8/43 (19)	4/43 (9)	Not reported	3+

Over the five-year study period, entry screening of 87,518 new prisoners identified 53/55 (96% sensitivity) TB disease cases in this group. (**3+**)

Another non-analytic study{382} reported on the following screening procedures to detect TB disease in new prisoners:

- routine tuberculin skin tests
- routine chest X-ray tests
- use of isolation for prisoners with suspected TB disease.

The evidence is presented in Table 54.

Table 54: Summary of evidence: process of detecting active TB in prisons

	Mantoux test screening period	Chest X-ray screening period	Statistical significance	NICE grade
Detection of cases treated for TB disease, N	8 (denominator not reported)	8/1,830	Not reported	3+
Average time to isolation of suspected TB cases, hours	Exceeded 96 hours	24 hours or less[yy]	Not reported	3+
Prisoners placed in isolation, N (%)	8/72 (11)	64/72 (89%)[zz]	Not reported	3+

yy Change in protocol from use of Mantoux test to use of chest X-ray screening eliminated the waiting period for reading Mantoux test results.
zz Only 7/16 inmates ultimately met the case definition for active TB disease for both periods.

12.3.5 From evidence to recommendations

Other than limited data on measures to enhance treatment for latent TB infection in prisoners in the USA, there was little good-quality data in this area. There was a small amount of data to suggest that questionnaires are better than X-rays on initial screening, but that chest X-rays were better for screening symptomatic patients during imprisonment.

It is important to raise awareness of signs and symptoms in prisoners, prison staff and healthcare workers working in prisons and remand centres.

A lack of continuity of care over transfer between prisons and release to the community was seen as a major barrier to treatment completion, and prison medical services should take responsibility for having arrangements in place before either transfer or release.

There is a risk of drug resistance and the possibility of non-adherence, and accordingly DOT is recommended for all prisoners and detainees.

In addition, there is a risk to prison staff, and a level of occupational health equivalent to that of healthcare workers is recommended.

The current practice of taking three sputum samples within 24 hours for microscopy, including a morning sputum sample is supported in the recommendations.

The GDG considered the possibility of screening and BCG vaccination in young offenders' institutions, but agreed that the low number of cases that would be detected could not justify this.

12.3.6 Recommendations

307. Healthcare professionals in prisons and immigration removal centres should ensure prisoners and detainees are screened for TB within 48 hours of arrival. [2012]

308. Prisons with Department of Health-funded static digital X-ray facilities for TB screening should X-ray all new prisoners and detainees (including those being transferred from other establishments) if they have not had a chest X-ray in the past 6 months. This should take place within 48 hours of arrival. [2012]

309. Prison and immigration removal centre health staff should report all suspected and confirmed TB cases to the local multidisciplinary TB team within 1 working day. [2012]

310. Multidisciplinary TB staff should visit every confirmed TB case in a prison or immigration removal centre in their locality within 5 working days. [2012]

311. If a case of active TB is identified, the local Public Health England unit, in conjunction with the multidisciplinary TB team, should plan a contact investigations exercise. They should also consider using mobile X-ray to check for further cases. [2012]

13 Glossary

13.1 Abbreviations

ACH
Air changes per hour

ADA
Adenosine deaminase assay

AFB
Acid fast bacilli

BCG
Bacille Calmette-Guerin

BTS
British Thoracic Society

CCDC
Consultant in communicable disease control or health protection

CDC
Centres for Disease Control

CI
Confidence interval

CNS
Central nervous system

CSF
Cerebrospinal fluid

CUA
Cost-utility analysis

DOR
Diagnostic odds ratio

Update 2015

DOT
Directly observed therapy

DOTS
Directly observed therapy short course

ESAT-6
Early secretory antigenic target 6

ETH
Ethambutol

FM
Fluorescence microscopy staining

GDG
Guideline development group

GRADE
Grading of recommendations, assessment, development and evaluation

GPP
Good practice point

HCW
Health care workers

HEPA
High efficiency particulate air filtration

HPA
Health Protection Agency (now superseded by Public Health England)

HTA
Health technology assessment

ICER
Incremental cost-effectiveness ratio

IgG
Immunoglobulin G

IgM
Immunoglobulin M

IGRA
Interferon gamma-release assay

INH; H
Isoniazid

ITT
Intent-to-treat

JCVI
Joint Committee on Vaccination and Immunisation

LAM
Lipoarabinomannan

LJ Slope
Lowenstein-Jensen Slope solid-media

LTBI
Latent tuberculous infection

MDR-TB
Multidrug-resistant tuberculosis

NAAT
Nucleic acid amplification test

NICE
National Institute for Health and Care Excellence

NMA
Network meta-analysis

OR
Odds ratio

PCR
Polymerase chain reaction

PHE
Public Health England

PPD
Purified protein derivative

PZA; Z
Pyrazinamide

QALY
Quality adjusted life year

RCT
Randomised controlled trial

RIF; R
Rifampicin

RR
Relative risk

SMI
Standards for Microbiology Investigations

SSM
Sputum smear microscopy

TB
Tuberculosis

TST
Tuberculin skin test

UVGI

Ultraviolet germicidal irradiation

WHO

World Health Organization

XDR-TB

Extensively drug resistant tuberculous

ZN

Ziehl-Neelsen microscopy staining

13.2 System for drug regimen abbreviations

Drug regimens for anti-TB treatment are often abbreviated according to the following system: a number indicating the length of a phase of treatment in months, followed by letters for the drugs administered in that phase. Consecutive phases are separated by a slash.

H = isoniazid

R = rifampicin

Rb = rifabutin

Rp = rifapentine

Z = pyrazinamide

E = ethambutol

Examples:

2HRZE/4HR is the standard ‘6 month, 4-drug regimen": 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin.

2HRE/7HR is 2 months of isoniazid, rifampicin and ethambutol followed by 7 months of isoniazid and rifampicin

Update 2015

2HRZ/7HR is 2 months of isoniazid, rifampicin and pyrazinamide followed by 7 months of isoniazid and rifampicin

2HRZ/4HR is 2 months of isoniazid, rifampicin and pyrazinamide followed by 4 months of isoniazid and rifampicin

13.3 Glossary

Acid fast bacilli

Bacteria which, having been stained with a dye, retain their colour in acid alcohol. Used as a technique for microscopic detection of mycobacteria.

Action plan

See ‘TB action plan’.

Active case-finding

Systematically identifying people with active or latent TB using tests, examinations or other procedures.

Active tuberculosis

Infection with mycobacteria of the M. tuberculosis complex, where mycobacteria are growing and causing symptoms and signs of disease. This is distinct from latent TB, where mycobacteria are present, and may be dormant, but are not causing disease. Symptoms include weakness, weight loss, fever, loss of appetite, chills and sweating at night. Other symptoms of TB disease depend on where in the body the bacteria are growing. If TB is in the lungs (pulmonary TB), the symptoms may include a cough, pain in the chest, and coughing up blood.

Adenosine deaminase assay

A test for TB based on the detection of adenosine deaminase activity in serum and plasma samples.

Adherence

The term adherence refers to the person's ability or willingness to adhere to a treatment regimen.

See also ‘Compliance’ and ‘Concordance’.

Update 2015

Adult

A person aged 18 years or more.

Atypical mycobacteria

Mycobacteria other than those of the M. tuberculosis complex.

Audit

See ‘Clinical audit’.

Automated liquid culture system

Automated systems allow continuous monitoring of cultures grown using a liquid medium (see ‘Liquid culture’). Time to detection is more rapid than traditional methods.

Bacille Calmette-Guerin vaccine

A vaccine for TB named after the French scientists Calmette and Guerin.

Bronchoalveolar lavage

A procedure for collecting respiratory samples from the airway, typically during bronchoscopy. Sterile saline is flushed through an airway, and the resultant mixture is aspirated for diagnostic investigation (for example, by microscopy or culture).

Cavitatory disease

A more advanced and infectious stage of pulmonary disease in which holes (‘cavities’) develop in the lung, resulting from the destruction of pulmonary tissue by direct bacterial invasion and an immune response.

Case-control study

Comparative observational study in which the investigator selects people who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Case series

Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of people.

Update 2015

Chemoprophylaxis

Treatment for latent TB infection. The administration of anti-TB drug(s) to prevent the acquisition or progression of tuberculosis infection. The former may be referred to as primary chemoprophylaxis or preventive therapy, the latter as secondary chemoprophylaxis.

Children and young people

A person aged 17 years or younger.

Class of recommendation

See "grade of recommendation".

Clinical audit

A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.

Chemotherapy

The antibiotic treatment regimens used to treat TB.

Cochrane review

A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.

Cohort study

A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case 2 or more groups are selected on the basis of differences in their exposure to the agent of interest.

Compliance

The extent to which a person complies with a recommended treatment regimen. In recent years use of the term compliance has been discouraged because of its connotations of patient subservience.

(See ‘Adherence’).

Concordance

The percentage of agreement between two tests.

Confidence interval

A range of values that contains the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.

Contact (domestic, close, casual, workplace)

A person who has spent time with a person with infectious TB.

Contact tracing

Identifying people who may have come into contact with a person with TB and assessing them for risk of significant exposure to TB. The aim is to find associated cases, to detect people with latent TB infection and to identify those not infected but for whom BCG vaccination might be appropriate.

Cost-effectiveness analysis

An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost–utility analysis

A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life years (QALYs).

Culture

The process of growing TB bacteria from sputum or other samples for identification and diagnosis.

Cure and completion rate

The proportion of people receiving treatment for active TB who either have negative culture results during the continuation phase of treatment, or who complete treatment without documented culture status.

Update 2015

Decision analytic model/techniques

A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.

Descriptive study

Observational studies or surveys designed to quantify current service provision or clinical conditions. Such studies are not designed to test hypotheses about the data.

Diagnostic odds ratio (DOR)

This is a single summary of diagnostic performance (it describes the ratio of the odds of a positive test result in a person with disease compared to a person without disease). The DOR can be calculated from sensitivity and specificity data and where a test provides no diagnostic evidence the DOR is 1.

Directly observed therapy (DOT)

A trained health professional, or responsible lay person supported by a trained health professional, provides the prescribed medication and watches the person swallow every dose.

Directly observed therapy short-course

The World Health Organization has developed a control strategy known as directly observed therapy short-course, which requires microscopy based diagnosis, standardised treatment under direct supervision, a secure supply of quality drugs and equipment, careful monitoring and supervision, and political commitment to support these activities.

Discordance

The percentage of disagreement between two tests.

Disseminated (including miliary) tuberculosis

Blood-borne spread of TB which may or may not be accompanied by chest X-ray or high resolution CT changes.

Environmental mycobacteria

Mycobacteria other than those of the M. tuberculosis complex.

Update 2015

Extrapulmonary disease

Active TB disease in any site other than the lungs or tracheobronchial tree.

Extensively drug resistant TB

Resistance to at least isonaizid and rifampicin, one injectable agent (capreomycin, kanamycin or amikacin) and one fluoroquinolone.

Gastric lavage (gastric washings)

Some people (particularly children) with suspected TB are unable to cough up any sputum. As an alternative, in a gastric lavage, saline solution is introduced into the stomach through a tube, the contents are pumped out and are examined for M. tuberculosis complex bacteria.

Genotypic testing

See ‘Molecular assays’.

Gold standard

See ‘Reference standard’.

Good practice point

Recommended good practice based on the clinical experience of the guideline development group (GDG) in the absence of robust, published clinical evidence.

Guideline development group

The guideline development group (GDG) agrees the clinical questions for the guideline, considers the evidence and develops the recommendations. The GDG membership is multidisciplinary comprising clinicians, patients and/or carers and technical experts.

Heaf test

A type of tuberculin skin test in which tuberculin is injected intradermally with a multiple puncture apparatus. The injection site is examined for signs of an immune response within 7 days. (Also see ‘Tuberculin skin test’ and ‘Mantoux test’).

Health Technology Assessment

These consider the effectiveness, appropriateness and cost of technologies and are funded by the NHS Research and Development Division.

Histology

Microscopic examination of cells and clinical samples.

Household contact

A person who lives in the same house as a person with infectious TB.

Immunocompromised

In this guideline, immunocompromised refers to a person who has a significantly impaired immune system. For instance this may be because of prolonged steroid use, TNF-α antagonists, antirejection therapy, the use of immunosuppression-causing medication or comorbid states that affect the immune system, for example HIV, chronic renal disease, many haematological and solid cancers and diabetes.

Incremental cost-effectiveness ratio

A measure of the additional cost of a health care activity per unit of benefit (usually a QALY, see below).

Index case

The initial person found to have TB, whose contacts are screened. Consequently, the source of their infection may be found, but the initial presenting patient is regarded as the index case.

Induration

The firm skin reaction occurring after the performance of a tuberculin skin test to diagnose latent TB infection. It is measured, and the result compared to guidelines to determine whether the test result is classified as positive or negative. This guidance recommends a threshold of 5 mm for tuberculin skin test positivity.

Infection control

Measures, other than screening, to minimise the risk of transmitting infections.

Infectious TB

Active sputum smear-positive pulmonary TB, that is with acid fast bacilli visible on microscopy. Active TB affecting other parts of the respiratory tract or oral cavity, though rare, is also considered infectious.

Update 2015

Intention-to-treat analysis

An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Interferon-gamma release assay

A blood test used to diagnose latent TB (which may be used as an alternative, or an addition, to tuberculin skin tests) based on detecting the response of white blood cells to TB antigens.

Isolation

An infection control measure in which people with infectious TB are kept away from others who may be at risk of infection. This guideline deals with 3 levels of isolation for infection control in hospital settings:

- negative-pressure rooms, which have air pressure continuously or automatically measured, as defined by NHS Property Services;
- single rooms that are not negative pressure but are vented to the outside of the building
- beds on a ward, for which no particular engineering standards are required.

Kappa Value

A measure of agreement of accuracy beyond chance.

Latent TB

Infection with mycobacteria of the M. tuberculosis complex, where the bacteria are alive but not currently causing active disease. Also known as latent TB infection, or LTBI.

Liquid culture

Culture grown using a liquid medium where mycobacteria grow faster (compared to solid media). (Also see ‘Automated liquid culture systems’).

Mantoux test

A type of tuberculin skin test in which tuberculin is injected intracutaneously. The injection site is examined for signs of an immune response after 2–3 days. (Also see ‘Tuberculin skin test’ and ‘Heaf test).

Update 2015

Meta-analysis

A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

Methodological limitations

Features of the design or reporting of a clinical study that are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.

Molecular assays

A process used to detect the presence of a particular genetic sequence in the cells of interest, using suitably labelled complementary sequences. In the case of TB, particular genetic sequences can confirm the mycobacterial species or the presence of certain drug resistance mutations.

Multidrug-resistant TB

TB resistant to isoniazid and rifampicin, with or without any other resistance.

Mycobacterium tuberculosis complex

The related mycobacterial species M. tuberculosis, M. bovis and M. africanum which can cause TB in humans.

Non-respiratory TB

Active TB affecting any part of the body other than the lungs, bronchi, pleura or thoracic lymph nodes (for example, the meninges or cervical lymph nodes).

Needs assessment

An assessment of the potential benefit from health care activities at a population-wide level. A needs assessment takes into account epidemiology, current service provision, and evidence of clinical effectiveness and cost-effectiveness.

Negative pressure room

Used for the isolation of certain patients known or suspected to have infectious TB. A negative pressure room is one where the air from the room is sucked out into

dedicated ducting through a filter and into the outside air, at a distance from all other air intakes. The level of pressure should be 10 pascals below the ambient pressure.

New entrant

Anyone coming to work or settle in the UK. This will include immigrants, refugees, asylum seekers, students and people on work permits. This group is intended to include UK-born people, or UK citizens, re-entering the country after a prolonged stay in a high-incidence country.

Non-household contact

A person who is in frequent contact with a person with infectious TB, in settings other than the home (such as the workplace or schools).

Nucleic acid amplification test

A test to detect fragments of nucleic acid, allowing rapid and specific diagnosis of M. tuberculosis directly from a range of clinical samples.

Odds ratio

A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The ‘odds’ is the ratio of non-events to events.

Opportunistic case-finding

Opportunistic identification of people with active or latent TB using tests, examinations or other procedures in the course of existing appointments or interactions, rather than identification through formal screening programmes.

Outbreak

There is no robust, widely accepted threshold for an outbreak of a disease, but in practical terms, an outbreak is the occurrence of an unusually high number of cases in associated people, in a small geographical area, and/or in a relatively short period of time.

Phenotypic drug susceptibility testing

The use of culture-based methods for drug susceptibility testing; that is, the culturing of M. tuberculosis in the presence of anti-TB drugs to detect growth (indicating drug resistance) or inhibition of drug (indicating drug susceptibility).

Update 2015

Post-primary TB

The stage following primary tuberculosis. This is when infection with the bacteria has advanced to disease, possibly symptomatic, with bacterial growth demonstrable by culture.

Primary TB

The initial stage of infection with TB bacteria, which is often asymptomatic, but can be detected by tuberculin conversion or interferon-gamma release assay.

Prison

Applies to any of state prison establishments, including young offender institutions.

Pulmonary disease

Active TB disease involving the lungs and/or tracheobronchial tree

Quality-adjusted life- year

An index of survival that is adjusted to account for the person's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost–utility analysis.

Randomised controlled trial

A comparative study in which participants are randomly allocated to intervention and control groups, and prospectively followed up to examine differences in outcomes between the groups.

Reactivation

The advancement of old latent TB (whether previously detected or not) into active TB.

Reference standard

An agreed standard, for example for a test or treatment, against which other interventions can be compared.

Relative risk

The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A, divided by the risk of the event in group B).

Rifampicin resistance

Resistance to rifampicin. Considered a proxy for multidrug resistance.

Schools vaccination programme

BCG vaccination programme performed in schools in children aged 10–14 years.

Sensitivity (of a test)

The proportion of individuals classified as positive by the gold or reference standard, who are correctly identified by the study test.

Short-course treatment

Modern 6 month treatment regimens for active TB (previously treatment had been for at least 12 months).

Standard recommended regimen

These guidelines recommend a drug treatment regimen using four different drugs over a duration of 6 months in people with active TB without central nervous system involvement. This is not applicable in all cases.

Skin test

See ‘Tuberculin skin test’.

Smear grading

The number of bacilli found in a sputum sample, believed to relate to the degree of infectivity of the person. There are several systems but in general recording goes from no acid-fast bacilli in 100 fields (0 or negative) to >10 acid-fast bacilli per field in at least 20 fields (grade 3).

Smear-positive

See ‘Sputum smear-positive’.

Specificity (of a test)

The proportion of individuals classified as negative by the gold (or reference) standard, who are correctly identified by the study test.

Sputum

Mucus expelled from the bronchi and lungs by coughing (or retrieved from gastric lavage, see above). Sputum is examined for TB bacteria by microscopic examination of a stained smear; part of the sputum can also be used for culture.

Sputum smear-positive ('Smear positive')

Respiratory TB in which mycobacteria ('acid-fast bacilli', AFB) have been seen in a stained smear of sputum examined under a microscope. Confirmation of the diagnosis requires culture to differentiate the organisms from atypical mycobacteria (those which are not in the M. Tuberculosis complex).

Standards for Microbiology Investigations

An evidence-based collection of recommended algorithms and procedures for clinical microbiology developed by Public Health England.

Systematic review

Secondary research that summarises the evidence on a clearly formulated question according to a predefined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

TB action plan

'Stopping Tuberculosis in England: An Action Plan from the Chief Medical Officer' (October 2004) is a Department of Health publication which sets out actions regarded as essential to keep TB under control.

Treatment failure

Failure of the prescribed drug regimen to eliminate the TB bacteria from the body. Demonstrated by a lack of clinical improvement, or by positive culture after the end of the fourth month of treatment.

Treatment interruption

A break in the prescribed anti-TB regimen for 2 weeks or more in the initial phase, or more than 20% of prescribed doses missed intermittently.

Tuberculin conversion

A change from a negative to a positive tuberculin skin test for latent TB.

Tuberculin skin test

Any one of a range of simple tests which inject tuberculin (purified protein derivative, [PPD]) into the skin. Immune reaction can be assessed after a few days according to the size of induration at the site of injection. They can demonstrate acquired immunity to TB, lack of immunity, or possible current infection (a strong response),

but are confounded by immunocompromise, serial TST, and prior exposure to atypical mycobacteria. The results are generally referred to as ‘positive’ or ‘negative’. (Also see ‘Heaf test’ and ‘Mantoux test’).

Xpert MTB/RIF assay

Cartridge-based, automated diagnostic test that can identify M. tuberculosis and rifampicin resistance by nucleic acid amplification.

Update 2015

14 References

For non-CCP review, the references to included studies can be found in the relevant appendix for each review

14.1 CCP reviews

14.1.1 Diagnosing active pulmonary tuberculosis: tests

Systematic reviews

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14.1.2 Diagnosing active pulmonary tuberculosis: collecting respiratory samples

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14.1.3 Diagnosing active extrapulmonary tuberculosis: tests

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